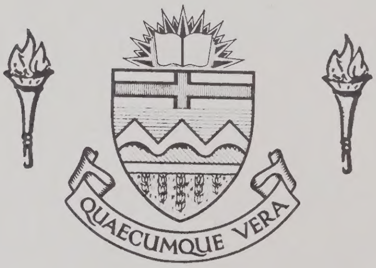
QUAECUMQUE VERA

THE UNIVERSITY OF ALBERTA

PANCREAS VISUALIZATION, A STUDY OF RADIOISOTOPE SCANNING TECHNIQUES AND COMPUTER ASSISTED DATA REDUCTION METHODS

by

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A THESIS

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ABSTRACT

A method of pancreas scanning employing a gamma camera, digital conversion of scan data, magnetic tape storage and computer processing of scan images, is described and evaluated as an aid to the diagnosis of pancreatic disease.

The radiopharmaceutical of choice for pancreas scanning is 75-Selenium-methionine which is not pancreas specific and accumulates in other organs, the most important of which is the liver. Elimination of the liver image is often necessary to permit adequate visualization of the pancreas and two methods of 'liver subtraction' are presented in this thesis; the first employing a 1600-channel analyzer, and the second with the additional use of a large digital computer.

Several display methods for the digital images and for the subtracted ('difference') images are presented.

Clinical follow-up of 114 patients has shown good correlation of scan interpretation with final clinical diagnosis.

It is concluded that pancreas scanning, employing the methods described, is a useful diagnostic tool in the investigation of the patient with suspected pancreatic disease.

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CHAPTER 1

INTRODUCTION

Radioisotope methods for organ visualization ('scanning') are based on the ability of the organ for differential uptake of a gamma-ray emitting radioisotope or radioisotope labelled material. Neoplastic, inflammatory and other disease processes in the organ result in altered patterns of radioisotope concentration and/or distribution. These changes are visualized by scanning techniques if the abnormal pattern is within the resolving power of the device used.

As the presence of pancreatic disease is often difficult to demonstrate by roentgenographic or laboratory methods it is not surprising that shortly after the introduction of organ scanning (1) research was directed to finding a suitable radioisotopic material which would concentrate in the pancreas.

In contrast to the thyroid, which was the first organ to be scanned, the pancreas proved to be a difficult problem. It exhibited no unique affinity for any available material such as was demonstrated by the thyroid for iodine. Many radioisotopes were evaluated but none showed adequate pancreatropism, or suitable radiation properties, until 75-Selenium-methionine was introduced in 1961 (2).

The necessity of an improved method for diagnosis

of pancreatic disease, and in particular pancreatic carcinoma, is immediately apparent when one considers that in the period 1953 to 1963 there were only four five-year survivors and no ten-year survivors in 398 cases of carcinoma of the pancreas registered in the Province of Alberta (3). A recent report of 257 cases of carcinoma of the pancreas studied in Connecticut (4) revealed only one five-year survivor and no ten-year survivor.

Unfortunately, the presence of early, and suppposedly curable, pancreatic malignancy is usually unassociated with a well defined symptomatology. It is in this early stage of the disease that pancreas scanning is of greatest value; i.e. in the investigation of patients with vague abdominal complaints, unexpected weight loss, unexplained thrombophlebitis and atypical depression (5) who harbour occult tumours of the pancreas. Patients with functioning adenomas of the pancreas (producing the Zollinger-Ellison syndrome and hyperinsulinemia), pancreatitis, pancreatic trauma, psuedocyst of the pancreas, recent onset of diabets, obstructive jaundice, metastases of unknown primary origin and malabsorption will also possibly benefit from the additional diagnostic information provided by a pancreas scan.

Brain, liver, lung, bone, spleen and kidney scanning have been established as useful and even necessary diagnostic procedures in clinical medicine. The validity of pancreas scanning however is not established in the minds of many clinicians, although most investigators who

evaluated the technique support it as being accurate and useful in the majority of cases.

Despite the many advances in the technology of scanning there are still many inherent problems which render the pancreas one of the most difficult, if not the most difficult, organ to scan. It is deeply situated in the posterior retroperitoneal aspect of the abdomen with considerable intervening soft tissue, which acts as a scattering medium, between it and the scan device. Although 75-Selenium-methionine is an acceptable radiopharmaceutical, it is far from ideal. The liver accumulates a significant amount of 75-Selenium-methionine and often overlaps and obscures the pancreatic image.

These problems, particularly the frequent need to eliminate the hepatic contribution to a pancreas scan, has stimulated the development of dual radioisotope techniques which will be described in Chapter 4.

It was the purpose of the present study to improve available methods of pancreas scanning and to develop a method of dual radioisotope scanning using the gamma camera with computer processing of the scan image. Representative cases, demonstrating the application of the method developed, will be presented as will be the correlation of clinical follow-up with scan diagnosis for 114 patients.

CHAPTER 2

RADIOISOTOPE AND RADIOISOTOPE LABELLED MATERIALS WHICH HAVE BEEN EVALUATED FOR PANCREAS SCANNING

2.1 Zinc

Several proteins found in the pancreas including insulin, uricase and carbonic anhydrase contain zinc and early investigators, attempting to find a radioisotope for pancreas scanning, naturally turned their attention to the readily available radioisotopes 62-Zinc and 65-Zinc. When orally or parenterally administered zinc is concentrated in the pancreas, liver, kidney and prostate (6,7). Aronow, Thors and Brownell (7) and Meschan et.al. (6) demonstrated however, that radioisotopes of zinc are unsuitable for pancreas scanning due to inadequate differential uptake by the pancreas.

2.2 Manganese

The element manganese was investigated by Meschan et.al. (6). Both 54-Manganese and 52-Manganese as the chloride showed inadequate concentration in the pancreas for purposes of scanning.

2.3 Localizing Antibodies

131-Iodine labelled antibodies for many tissues show marked tissue specificity and high concentrations have been found in some target organs (6). This is not true of

the pancreas, however, and attempts to produce a labelled pancreatic antibody for scanning purposes have been unsuccessful (6,8).

2.4 Secretin-like Polypeptide (S.P.)

A synthetic polypeptide composed of 27 amino acid with secretin-like properties (elevation of pancreatic bicarbonate and fluid secretion) has been labelled with 131-Iodine and has shown some pancreatic specificity, but attempts to produce an adequate specific activity of 131-Iodine for purposes of scanning have been generally unsuccessful (6,8). Attempts to label S.P. with 99m-Technetium (9) showed some initial promise but again specific activity has been a problem and tissue specificity may in fact be destroyed in the labelling process.

In the event that labelling is more successful, it is still doubtful that a labelled S.P. of adequate specific activity can be produced which will avoid undesirable hormonal side effects.

2.5 Berberine

Berberine is an alkaloid obtained by alcohol extraction of an African herb, Columbo Root. Nardie and Seipel using fluorescent methods suggested remarkable pancreatic affinity for Berberine (10). However, quantitative evaluation showed no selective localization in pancreatic tissue either when labelled with 131-Iodine or in the

unlabelled form (11).

2.6 Cesium

131-Cesium produced from a 131-Barium/131-Cesium generator was suggested by Sodee (12) as a suitable radioisotope for pancreas scanning on the theory that ionic cesium would be concentrated in preference to potassium, but inadequate differential concentration of cesium in the pancreas is obtained for purposes of scanning.

2.7 131-Iodine Labelled Macroaggregates of Human Serum Albumin (IMAA)

King et.al. (13) introduced the concept of injection of IMAA at the time of celiac axis arteriography to allow scanning of the abdomen following the angiographic procedure. Ogris et.al. (14) and Johnson et.al. (15) have reviewed this technique and although the injection of IMAA via the celiac axis or by selective arterial injection can often produce good pancreatic visualization by scanning, the variability of the blood supply to the pancreas and the non-specific distribution of macroaggregates, in this technically difficult procedure, has limited its usefulness.

2.8 Toluidine Blue

It has been noted (16) that the pancreas and parathyroids show apparent remarkable affinity for Toluidine

Blue when it is injected intravenously. The material has been successfully employed to localize the parathyroids at the time of thyroidectomy and to aid visualization of the pancreas at the time of abdominal surgery (17,18). Unfortunately attempts to label Toluidine Blue with 131-Iodine and 99m-Technetium decolour the material and destroy tissue specificity. If a suitable label can be found for Toluidine Blue, this material may prove to be of considerable use in pancreas and parathyroid scanning.

2.9 Amino Acids

Tarver and Schmidt in 1942 (19) described the distribution of 35-Sulfur labelled methionine in the rat and dog. Their experiments showed that most of the methionine was used in metabolism of proteins and of those tissues assayed, the greatest total amount was found in the liver. It has subsequently been shown that hepatic uptake is used mainly for structural protein or plasma protein synthesis and only a small amount is excreted in the bile (20). It was also noted by Tarver and Schmidt that a high concentration was found in the pancreas.

In 1949, Wheeler et.al. (21) demonstrated that pancreatic uptake of methionine occurred mainly in the exocrine pancreas.

In 1953, Allfrey, Daly and Mirsky (22) demonstrated uptake of intravenously administered 15-Nitrogen glycine in the pancreas and liver of experimental animals

and in 1955 the same authors (23) showed the high concentration of intravenously administered 15-Nitrogen glycine in trypsinogen and chymotrypsinogen in the mouse pancreas.

Hansson (24) in a comprehensive review and investigation, described the use of radioisotope labelled amino acids in the study of pancreatic metabolism and outlined the time course of uptake, concentration and excretion of a number of amino acids. He demonstrated that the concentration of amino acids when injected intravenously reached a high level in the pancreas within minutes, with a peak concentration achieved in about 30 minutes. 35-Sulfur labelled methionine, 35-Sulfur labelled cystine, 14-Carbon labelled phenylalanine and 14-Carbon labelled glycine were investigated.

Blau (2) studied radioisotope labelled tryptophane, methionine, cystine, phenylalanine and glycine. Of the amino acids studied, the pancreas showed the greatest affinity for tryptophane. It was also shown that the concentration of tryptophane was greatest in the pancreas relative to all other organs. In the rat approximately 12% of an intravenous dose of tryptophane was found in the pancreas about one hour post-injection. Tryptophane is followed closely by methionine and cystine in this regard.

Unfortunately none of the elements of amino acids (carbon, hydrogen, oxygen and sulfur) have gamma emitting radioisotopic forms suitable for scanning.

In 1961 Blau (25) suggested that the selenium analogue of methionine might be useful for pancreas scanning. 75-Selenium, which has suitable gamma emissions for scanning, was used in the biosynthesis of selenium-methionine and selenium-cystine (25,26). Blau demonstrated that, in many animals, pancreatic specificity for selenium-methionine was essentially the same as for methionine (2,8). The first clinical use of 75-Selenium-methionine as a pancreas scanning agent was reported in 1962 by Blau, Manske and Bender (27).

Since 1962, 75-Selenium-methionine has been used for virtually all routine pancreas scanning although 75-Selenium-cystine is also available (28).

131-Iodine labelled phenylalanine has shown some pancreatic specificity and has been successfully labelled. However, the specific activity of the labelled product and the concentration achieved in the pancreas has not been satisfactory (29).

Tryptophane does not contain sulfur and therefore cannot be prepared as a selenium analogue. Iodination of tryptophane destroys normal metabolic activity and 131-Iodine labelled tryptophane shows no pancreatic specificity (8).

2.10 Preparation of Selenium-Methionine

Although chemical synthesis of the selenium analogue of various sulfur containing amino acids had been achieved

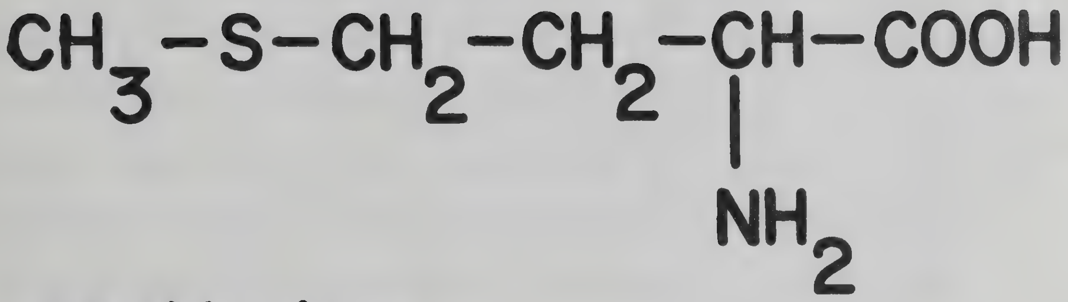
previously, Blau (25) and Tuve et.al. (26) demonstrated that biosynthesis gave a better yield with more convenient preparation.

Blau described the use of yeast (Saccharomyces cerevisiae) grown on a low sulfur content culture medium containing 75-Selenium as H_2SeO_3 of up to 10 millicuries per litre (mCi/L) concentration. The micro-organism synthesized the selenium analogue of methionine (Figure 2.10.1) with no apparent differences in morphologic or cultural characteristics. Hydrolysis of the protein content of the culture medium, and subsequent column separation, produced the various amino acids.

This biosynthetic procedure has been modified by the use of other micro-organism for more efficient production of selenium-methionine, but the basic method remains similar to that described by Blau (25) and Tuve et.al. (26).

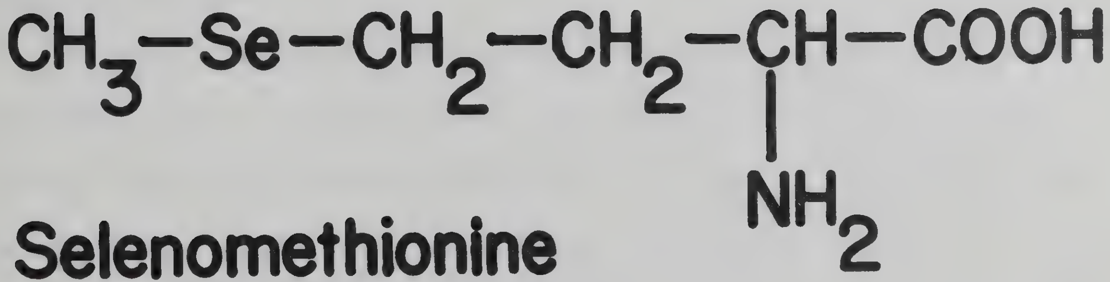
2.11 Properties and Organ Distribution of Selenium-Methionine

Several investigators have shown the almost identical biochemical and metabolic function of selenium-methionine, in animals and humans, as compared with methionine (20,30). Selenium-methionine is a naturally occurring trace amino acid in humans and animals. It is found in high concentrations in a number of plants (31). When administered to animals



$$CH_3-S-CH_2-CH_2-\underset{\displaystyle NH_2}{\underset{|}{CH}}-COOH$$

Methionine



$$CH_3-Se-CH_2-CH_2-\underset{\displaystyle NH_2}{\underset{|}{CH}}-COOH$$

Selenomethionine

FIG. 2.10.1

selenium-methionine takes part in virtually all metabolic functions involving protein synthesis (8,32).

It readily crosses the placenta and is secreted in milk protein (32).

75-Selenium-methionine when injected intravenously shows rapid accumulation in liver, pancreas, G.I. mucosa, bone marrow, parathyroid, muscle, salivary glands and prostate (32,33) where it is used primarily for protein synthesis in these tissues and is incorporated into proteins at essentially the same rate as methionine. When ingested orally it crosses the intestinal wall at the same rate as methionine (8).

Incorporation into hemoglobin (34,35) and plasma proteins (36) has been extensively investigated as a measure of red cell and protein kinetics. Its use in the investigation of hemoglobin metabolism has been suggested (34) as it has been found that selenium-methionine appears as a significant proportion of hemoglobin amino acid content several days following intravenous injection of a tracer dose.

It has been demonstrated that selenium-methionine also shows significant uptake by malignant tissues, particularly lymphomas, (37,38) where protein synthesis is a characteristic of the tumour. Uptake in carcinomas, bone tumours and other sarcomas has been demonstrated (37,39) and its use as a general tumour scanning agent has been suggested (39). Malignant thymomas (40) have also been

demonstrated with 75-Selenium-methionine and its use in all cases of adult myesthenia gravis has been suggested as 15-30% of these patients harbour malignant thymomas.

It has been suggested (41) that liver function can be evaluated by measuring exhaled volatile metabolic products of 75-Selenium-methionine, mainly in the form of dimethyl selenide.

There are many reports of the successful demonstration of parathyroid adenomas using 75-Selenium-methionine (33,42,43,44,45,46,47,48) in hyperparathyroidism.

75-Selenium-methionine is incorporated into the exocrine pancreatic secretions mainly in the protein enzymes; trypsinogen, chymotrypsinogen, amylase, trypsin, lipase and ribonuclease. It appears that protein synthesis occurs in the microsomal fraction of the pancreatic cell and is stored and released in the zymogen granule (24).

A small amount of selenium-methionine is utilized in insulin metabolism but the rate of incorporation is so small as to be insignificant in the overall pancreatic uptake (21). An exception is seen in functioning insulinomata and tumours associated with the Zollinger-Ellison syndrome where adequate uptake may occur to present as a 'hot' spot in a pancreas scan (49,50).

Sodee et.al. (51) have shown, in the dog, that the pancreas:liver ratio is approximately 6:1 during the first four hours post administration. Blau suggested that the ratio was 8.8:1 in dogs (8). These figures,of course, cannot be

verified in humans with normal pancreatic tissue.

75-Selenium-methionine is very stable chemically in aqueous solutions at normal temperatures if protected from oxidation (8). Very little radiolysis of the material occurs and no detectable decomposition or racemization is seen when stored for several months at 20° C with an initial specific activity of one curie per milliMole (Ci/mM) (52).

To date no reports of allergic or other deleterious reactions to the intravenous administration of 75-Selenium-methionine have been published.

75-Selenium-methionine is commercially available in a specific activity of approximately 10-20 milliCuries per milligram (mCi/mg).

2.12 Technetium Labelled Methionine

Tubis and Endow (9,53) in 1967 reported 99m-Technetium labelling of methionine and cystine and a secretin-like polypeptide (S.P.). Technetium labelling of methionine would overcome the most important inherent disadvantage of 75-Selenium-methionine, i.e. a long physical and biological half life. Unfortunately, preliminary experimental evaluations of 99m-Technetium labelled amino acids and S.P. have been equivocal at best.

2.13 Selenium

There are six stable nuclides of selenium and approximately twelve radionuclides with five additional metastable states (54). Selenium is a trace metal in humans

(31) and can produce toxicity if administered in high doses. It produces a well known disease - alkali disease or 'blind staggers' - in cattle when seleniferous plants are ingested in excess. Livestock exhibit slow growth and degenerative myopathies in selenium deficiencies but this disease has not been reported in humans. Three milligrams per kilogram has been reported as a lethel dose in a few hours in animal experiments (41). Considerable attention has recently been directed to the metabolism of selenium (55,56,57,58).

The gamma emitting radionuclide 75-Selenium has a 120 day half life with relatively 'clean' major gamma emissions of 136, 265 and 280 KeV. It decays by electron capture and the daughter nuclide is stable 75-Arsenic (Figure 2.13.1).

The amount of selenium found in commercial preparations of 75-Selenium-methionine is only a few micrograms and does not constitute a toxic hazard (8).

75-Selenium as selenate has been investigated as a non-specific tumour localizing agent in animals and man with poor results (37,59).

Intravenous 75-Selenium has also been suggested as a sensitive indictor of liver function by measuring volatile dimethyl selenide exhaled in the breath (56).

2.14 Liver Scanning Agents

In the technique of pancreas scanning to be described in this thesis, it is necessary that a well-defined scan image

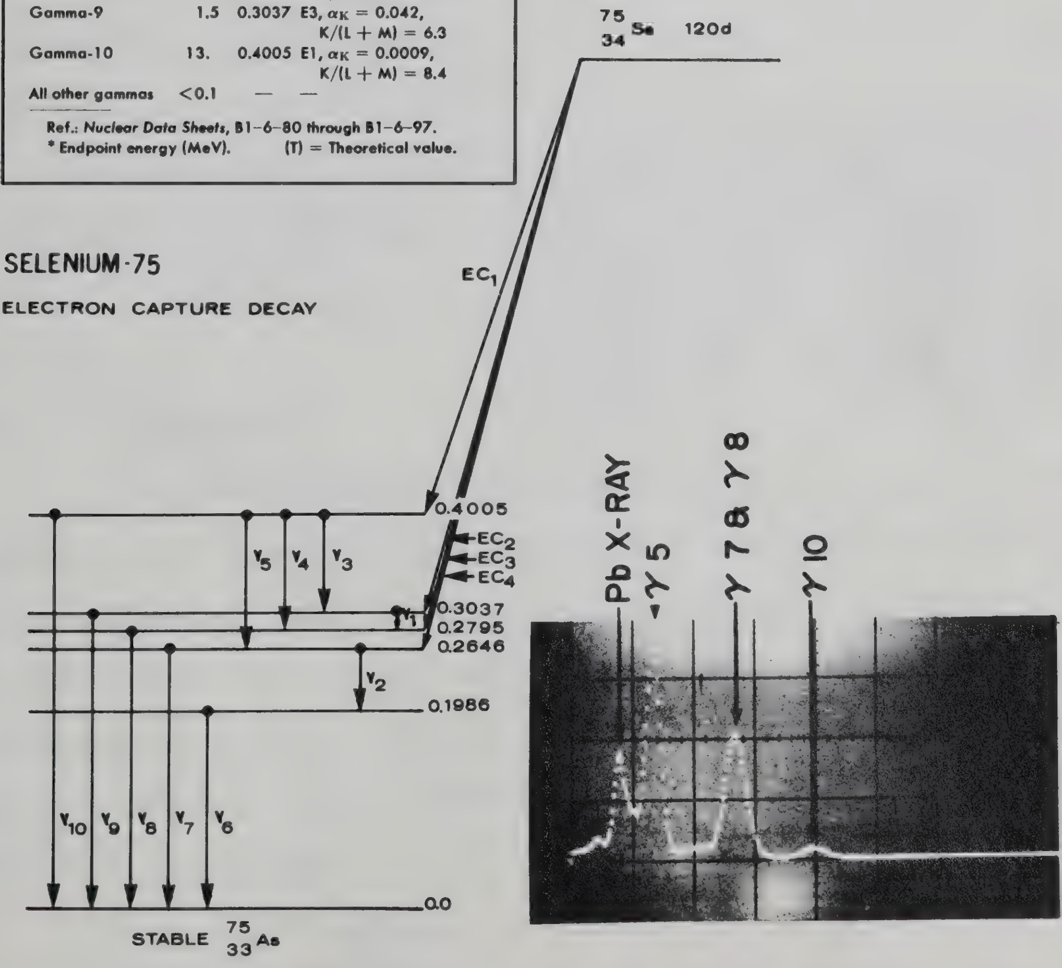
INPUT DATA

Radiation	%/dis-integration	Transition energy (MeV)	Other nuclear parameters
Electron capture-1	93.	0.464	Allowed
Electron capture-2	1.2	0.561	Second forbidden
Electron capture-3	2.6	0.585	First forbidden
Electron capture-4	3.5	0.600	First forbidden
All other electron captures	<0.1	—	—
Gamma-1	5.6	0.0245	M2, $\alpha_K = 159$ (T), $K/L = 3.7$, $K/M = 15.2$
Gamma-2	1.3	0.0660	M1, $\alpha_K = 0.28$, $K/L = 8.3$, $K/(L + M) = 6.9$
Gamma-3	5.8	0.0967	E2, $\alpha_K = 0.77$, $K/L = 7.5$, $K/(L + M) = 6.3$
Gamma-4	17.	0.1211	E1, $\alpha_K = 0.035$, $K/(L + M) = 8.6$
Gamma-5	57.	0.1359	E1, $\alpha_K = 0.025$, $K/L = 10.1$, $K/(L + M) = 8.6$
Gamma-6	1.4	0.1986	M1 + E2, $\alpha_K = 0.022$, $K/(L + M) = 8.6$
Gamma-7	59.	0.2646	M1, $\alpha_K = 0.0063$, $K/(L + M) = 10.2$
Gamma-8	25.4	0.2795	M1 + E2, $\alpha_K = 0.0077$, $K/(L + M) = 8.7$
Gamma-9	1.5	0.3037	E3, $\alpha_K = 0.042$, $K/(L + M) = 6.3$
Gamma-10	13.	0.4005	E1, $\alpha_K = 0.0009$, $K/(L + M) = 8.4$
All other gammas	<0.1	—	—

Ref.: *Nuclear Data Sheets*, B1–6–80 through B1–6–97.
* Endpoint energy (MeV). (T) = Theoretical value.

SELENIUM-75

ELECTRON CAPTURE DECAY



-FIG. 2.13.1-

of the liver be obtained. Radio-colloids which localize in the reticuloendothelial system of the liver are therefore employed.

198-Gold as an elemental colloidal preparation has been used for several years for liver scanning. 198-Gold has a physical half-life of 64.8 hours and, in common with other radio-colloids, the biological half-life is equal to the physical half-life, as the material is sequestered in the reticuloendothelial system indefinitely. It has a useful major gamma emission of 412 KeV (Figure 2.14.1).

99m-Technetium as a technetium-sulfur colloid presents several advantages over 198-Gold colloid as discussed in Section 6.2, and has recently found general acceptance for liver scanning. 99m-Technetium has a 6.1 hour physical half-life and a major gamma emission of 140 KeV (Figure 2. 14.2).

2.15 Dosimetry

The dosimetry of 75-Selenium-methionine when injected intravenously cannot be calculated with complete accuracy as the effective half-life in critical organs and indeed in the whole body is variable from person to person. Estimates and measures of the effective half-life vary between 21 days (60) and 150 days (61). Most estimates range from 50 to 100 days (8,41,62,63,64).

Blau (27) initially estimated the effective half-life in rats and mice at 15 to 20 days and suggested that the

value was similar in humans. He later revised his estimate of the effective half-life to about 100 days in humans (8). With this value he estimated the whole body dose to be 1.3 roentgens (R), the pancreatic dose 1.4 R and the liver dose 1.4 R when 250 microCuries (µCi) of 75-Selenium-methionine were injected in a 70.0 kilogram (Kg) human.

Other estimates of whole body dose range from 0.9 R (60) to 2.3 R (51). This latter value was estimated by Sodee on the basis of tissue distribution studies in animals and an effective half-life of 67.5 days with an administered dose of 250 µCi in a 70.0 Kg human.

The critical organ is the kidney but the renal dose of 14.5 R calculated by Sodee is certainly too high as it is estimated on the basis of 80% excretion in the urine averaged over the entire half-life.

For purposes of comparison it might be noted that an average brain scan delivers approximately 0.12 R whole body dose and 0.96 R to the colon (65) for 10 mCi of intravenous 99m-Technetium with perchlorate administration.

3.0 mCi of 99m-Technetium sulfur colloid delivers approximately 0.05 R whole body dose, 0.7 R liver dose and 0.07 R bone marrow dose (65).

150 µCi of 198-Gold colloid delivers approximately 0.35 R whole body dose, 5 R liver dose and 0.7 R bone marrow dose (65).

CHAPTER 3

METHODS TO ENHANCE PANCREATIC VISUALIZATION AND TO REDUCE ABSORBED DOSE

3.1 The Blau Protocol

In his initial description of pancreas scanning in 1962 (27) Blau referred to a protocol for patient preparation which he felt would enhance pancreatic uptake of intravenously administered 75-Selenium-methionine. He later (66) described this protocol in detail.

> After an overnight fast, a light breakfast consisting of two glasses of milk was given. Milk protein provided other amino acids for protein synthesis. Three hours later an intravenous dose of Cecekin (one unit per Kg) was administered intravenously. Cecekin is a mixture of cholecystokinin, secretin and pancreozymin. This was administered to stimulate initial secretion of pancreatic enzymes by the hormonal action of secretin and pancreozymin (cholecystokinin plays no part in pancreatic emptying but was present in this hormonal preparation, which was the only one available at that time). One hour later 75-Selenium-methionine (3 uCi/Kg) was given intravenously, with 15 mg of Probanthine orally.

> Probanthine inhibited pancreatic secretion for the duration of the study. One half hour later the scan was commenced.

This protocol was rather unwieldly and many patients complained of abdominal cramping, nausea and vomiting, presumably due to pancreozymin, and other investigators suggested modifications.

An example of how much uncertainty was associated with the usefulness of Blau's protocol is demonstrated by the various attitudes taken by Sodee. In reporting his first series of pancreas scans in 1964 Sodee (60) stated that he abandoned the Blau protocol after initial use and devised the following protocol.

> A high protein meal was followed in one hour by intravenous 75-Selenium-methionine and 15 minutes later by glutamic acid hydrochloride, with the scan begun immediately thereafter.

In 1965 (51) Sodee, on the basis of animal experiments, abandoned all protocol and scanned shortly after the intravenous administration of 75-Selenium-methionine. In 1966 (67,68) however he resumed his modified protocol as he felt the protein meal enhanced clearance of 75-Selenium-methionine from the blood and in 1967 (69) again abandoned this in favour of 35-gram glucose intravenous infusion

followed one half hour later by 75-Selenium-methionine. Later in 1967 (70) he once again reversed his stand and began scanning immediately after 75-Selenium-methionine with no preparation.

3.2 Morphine

Rodriquez-Antunez in 1964 (71,72) suggested the use of morphine to induce spasm of the sphincter of Oddi and to prevent pancreatic secretion. His protocol consisted of a light fat-free breakfast followed one half hour later by slow intravenous infusion of 75-Selenium-methionine and one-quarter grain of morphine intramuscularly. The scan was started immediately. In 1967 (73) he discontinued the use of morphine and suggested that it did not enhance pancreatic accumulation or retention of radioisotope.

3.3 Other Protocols

Haynie et.al. in 1964 (74) favoured a slightly modified Blau protocol but in 1965 (75) suggested that it was unnecessary and had little effect upon the final scan appearance.

Burke et.al. in 1964 (76) suggested methionine by mouth, 12 grams, for five to seven days prior to scanning to block the liver uptake of 75-Selenium-methionine. This would possibly allow better visualization of the pancreas and enhance pancreatic uptake of 75-Selenium-methionine. Preloading with methionine would presumably not affect the

pancreas to the same extent as the liver, as the turnover of proteins in the pancreas is much faster.

King et.al. in 1966 (77) reviewed the various protocols and concluded that in all probability no patient preparation was needed and seriously suggested that if pancreatic stimulation is needed, whiskey be substituted for Cecekin. Brown et.al. (64) stated that milk and Probanthine should be used but Kakehi et.al. (78) reported a large and very successful series of pancreas scans from Japan in which no patient preparation was employed.

Eaton et.al. (79) in 1967 pointed out on the basis of animal experiments that ethionine, the ethyl analogue of methionine, when given in small amounts produced a significant increase in ultimate pancreatic concentration of 75-Selenium-methionine with no significant increase in radioactivity in other organs. This appears to be the result of suppression of the acinar cell enzyme release rather than increased amino acid uptake or protein synthesis. Experimentally one milligram of ethionine per kilogram of body weight was used in rats. However in larger doses administered chronically, ethionine is carcinogenic and in doses of one gram per kilogram of body weight, acute administration of ethionine will produce experimental pancreatitis and other cytopathic effects in animals. Due to its toxicity, ethionine has not been used clinically.

It has been suggested (76) that post scanning 'flushing' of the patient with intravenous methionine should

be used to decrease the absorbed dose by enhancing excretion of the labelled methionine. This hypothesis has never been proven by experimental or clinical investigation.

It has also been suggested (80) that an intravenous infusion of a mixture of amino acids prior to scanning would enhance pancreatic uptake of selenium-methionine by making all necessary amino acids immediately available for protein synthesis.

In 1968 and 1969 (81,82) Reuter et.al. reported the use of celiac axis injection of 75-Selenium-methionine at the time of celiac axis angiography in an attempt to increase the uptake of 75-Selenium-methionine by the pancreas. There was evidence to suggest that increased uptake was achieved in the pancreas, but due to the variability of the arterial supply, there were occasions when incomplete visualization occurred (83). Also of uncertain significance was the effect of previous administration of contrast media upon pancreatic uptake of the radiopharmaceutical. The author suggested that 75-Selenium-methionine pancreatic scanning following celiac axis injection of the radiopharmaceutical might be of use, but is limited to those situations where angiography is being employed as the primary procedure.

Rodriquez-Antunez (72), early in his investigation of pancreatic scanning, suggested in those cases where the liver edge overlapped the pancreas, that visualization of the pancreas could be improved by rotating the patient into a slight left anterior oblique position to separate the pancreas

and liver edge, as viewed by the detector.

CHAPTER 4

DUAL RADIOISOTOPE METHODS FOR VISUALIZATION OF THE PANCREAS

4.1 Sequential Scans

Aronow, Thors and Brownell in 1959 (7) in describing their attempts to visualize the pancreas with ionic and complexed 62-Zinc also suggested the use of chelated 64-Copper to demonstrate the liver. In these studies a special rectilinear positron scanner, designed originally for positron brain scanning, was utilized. Two sequential scans were obtained; the first after the administration of the zinc compound and the second after the administration of the copper compound. The two scans were compared visually but unfortunately as previously indicated (Chapter 2) the zinc compound showed insufficient pancreatic specificity for clinical use.

In 1964 Sodee (60) reported a large series of pancreas scans using 75-Selenium-methionine and suggested that the liver contribution in the 75-Selenium-methionine scan could be effectively prevented in most cases by shielding the liver with lead sheets. This required a previous 198-Gold colloid scan to localize the liver edge. There were a small number of cases where pancreatic visualization could not be achieved as the liver edge overlapped and obscured the pancreas.

Schepers and Winkler (84) introduced the concept of electronic subtraction of the liver contribution from a 75-Selenium-methionine liver and pancreas scan. Their technique was to store all scanning data from a special rectilinear

scanning device onto punched paper tape and to subsequently process this information by digital computer. To facilitate the subtraction they suggested two sequential scans, one with 131-Iodine labelled Rose Bengal for the liver and the second with 75-Selenium-methionine for the liver and pancreas. They presented the results of phantom studies but did not report the use of the technique in clinical work.

4.2 Simultaneous Scans

As a footnote to their work Schepers and Winkler (84) suggested simultaneous dual channel recording of the two isotopes for subsequent subtraction but did not elaborate on this technique.

Spencer and Seive (85) reported a device for dual channel simultaneous scanning of two radioisotopes with different energies, and made specific reference to pancreas scanning. Their analogue device, attached to the output of a modified commercial rectilinear scanner, allowed the difference image (the pancreas image) to be developed as the scan proceeded (86,87) but they did not report on clinical material. Burn in 1967 (88) described a similar analogue device and suggested its use with a color print-out to differentiate data levels.

Kaplan et.al. (89) in 1966 reported the first clinical use of a dual channel rectilinear scanner for simultaneous scanning. The radioisotopes employed were 198-Gold colloid and 75-Selenium-methionine. The ratio of

75-Selenium to 198-Gold was determined over a portion of the liver anatomically separated from the pancreas and only those areas where this fixed ratio was exceeded, i.e. the pancreas, was displayed on the developed photoscan. Considerable success was achieved with the method in this, and subsequent, reports (90,91).

Eaton et.al. developed a similar subtraction device using a completely analogue method for electronic subtraction (92).

Ben-Porath, Clayton and Kaplan reported the use of simultaneous dual radioisotope studies with color representation of the two radioisotope distributions, and combination of subtraction and color display with apparent enhanced readability of the resulting paper dot scan (93). The same group also reported the storage of scan data on magnetic tape directly from the scan device. The tapes were later replayed and the information displayed on a CRT specially equipped with color filters to produce a color Polaroid photograph giving a representation of the distribution of the two radioisotopes simultaneously. This technique allowed storage of total scan information and playback, with the ability to vary the scan parameters, for optimum scan presentation. Clinical correlation of this technique in 109 patients was reported in 1969 (94).

4.3 Scintillation Camera

The first reported use of the scintillation camera for pancreas scanning was by Powell et.al. in 1966 (95).

The first and only reported use of a subtraction technique using the gamma camera was by Blanquet et.al. (96,97,98) using a 4096 multi-channel analyzer for storage of the digitized scan data. Their technique is very similar to that described in Section 6.5.

CHAPTER 5

DATA STORAGE, COMPUTER PROCESSING AND DISPLAY METHODS

5.1 Primary Storage and Display Methods

The first devices to determine the distribution of radioisotope were hand-held Geiger-Muller (G.M.) tubes. Counts were determined over an area of the body for a preselected time and a 'map' of the count rates was made by writing count rate values on a graphic representation of the patient.

The first report of an automatic rectilinear scanner was by Cassen et.al. in 1951 (1). This device used a calcium tungstate crystal and photomultiplier detector rather than a G.M. tube. The data display was in the form of ink marks placed on paper by vibrating pen. This pen was driven by a scaler to produce a mark for each of a preset number of counts detected. The marks on the paper gave an arithmetic representation of the counts detected but with this technique there was a problem of low contrast in areas of small count rate difference.

Basic rectilinear scanning devices have undergone relatively minor modifications over the past 20 years. However, improvements in data storage, processing and display have provided a considerable increase in flexibility and versatility to scanning procedures.

Horwitz (99) described the use of a flashing stroboscopic light to expose photographic paper. No mechanical

parts or electronic scaler were necessary for this display method but the display (dot density) again tended to bear a direct arithmetic relationship to the count rate detected.

Kuhl in 1956 (100) described the use of a count rate modulated glow tube to expose X-ray film. The density response of X-ray film is such that enhanced contrast over areas of limited count rate difference could be achieved. By adjusting the threshhold which activated the device, a degree of background subtraction was also possible.

Bender (101) using a tungsten filament light source was able to increase contrast on X-ray film to an even greater extent. This type of recording device (which is referred to as a 'photoscan') is now used in most commercially available rectilinear scanners for immediate display of the scan data.

In 1958 Anger (102) described a stationary imaging device (the gamma camera) in which a cathode ray tube (CRT) was used to display scintillation events as they occurred. Integration of these data for final display was achieved with an ordinary photographic time exposure, For purposes of conveniences, Polaroid film is now generally used for the immediate storage and display of scan data with this instrument (103).

5.2 Rescanning

It became apparent over the years that both the X-ray film used with rectilinear scanners and the Polaroid

film used with scintillation cameras were not completely satisfactory for recording and display of scan data. This was due primarily to technical errors in selecting display parameters (such as background subtraction and contrast enhancement) resulting in a poor scan and loss of scan information. It was also apparent that the unaided human eye could not appreciate all the information present in a well exposed film and that the film could not record all the information delivered to it. The dynamic response range offered by the photoscan is at best two orders of magnitude and it has been shown to be a self degenerative display because the eye is less able to detect differences in optical density in the higher density ranges, particularly above 1.5 (104). For purposes of enhancing the information present on X-ray film, various rescanning devices were devised in which combination of densitometer, black and white television display, color television display (105) and flying spot digitizer were employed (106). Various methods of count rate modulated color display, both on paper and photographic film, have been developed to enhance the contrast and 'readability' of rescanned data (107).

5.3 Complete Data Storage and Computer Processing

Many workers have felt that all data sensed by the detection device should be stored to prevent loss of data and to allow later manipulation for optimal representation (108). To this end, paper tape, magnetic tape and other

types of storage were developed. This stored data is usually replayed through the scan device with selection on a trial and error basis of optimal display parameters. It was realized at an early stage in these studies that the data could also be processed by computer methods.

The computer approach to scan analysis and display essentially treats the scanner as a transducer and as little as possible is done to permanently alter the accumulated scan information (109). The data is therefore stored in a non-destructive manner e.g. on magnetic tape.

The first application of computers to clinical scanning procedures was for the correction of collimator response in focussing systems and the correction of 'scalloping' effects inherent in rectilinear scanners.

The most useful application of the computer however, was for statistical evaluation and processing of the data. This type of information processing for radioisotope scans improves the signal to noise ratio with resulting image enhancement but without degradation of information content.

In 1964 Brown (110) reported the use of a high speed punched paper tape to store energy selected scintillation events and positioning data from a modified commercial rectilinear scanner, for later processing by digital computer. Data averaging techniques were used and alphanumeric (symbolic density) typewritten plots of the

processed scan data were obtained. As all information was permanently stored, the scan could be redisplayed to give optimum visualization by varying the programme parameters selected by the operator.

As previously mentioned, Schepers and Winkler (84) described a fast paper punched storage system with computer processing of the scan data obtained with a custom rectilinear scanner. The scanning device was a specially built incremental system with point by point, preset count scanning to reduce statistical error. Computer analysis included: subtraction of background, correction for radioactive decay, spatial averaging for each point and print-out of points as numeric values to allow isocount contours to be drawn by hand or to drive an automatic isocount plotter.

An evaluation of various computer techniques and display methods has been made by Tauxe et.al. (108,109,111). These authors also described their own method of magnetic tape storage and scan data for computer processing. A typewritten symbolic density plot or a Calcomp plot with up to 100 isocount levels could be obtained with their technique. However, the symbolic density plot did not give a true density representation of count rate but merely served to illustrate isocount contours. Although a digital computer was used for data storage, no numeric processing of data was carried out.

Since that time many reports have appeared describing various combinations of paper tape, magnetic tape, computer processing, typewriter or line printed symbolic density plots, Calcomp contour plots, CRT and photographic displays, television displays and three-dimensional isometric displays (112,113,114,115,116,117,118,119).

Reviews of digital computer applications in Nuclear Medicine have been given by Smith and Brill (120) and by Robertson (121).

5.4 Scintillation Camera Data Storage and Processing

The scintillation camera as developed by Anger, required more sophisticated methods for storage of scintillation pulses and positioning signals since they occur in a random fashion. Polycin (122,123) used a dual channel analogue to digital converter (ADC) and 1600 channel multiparameter analyzer for temporary storage and display of the scan image. Blanquet et.al. (96,97,98,124) described the use of 4096 channel analyzer for storage and display of scintillation camera data.

Camera/computer combinations have recently been made commercially available but in these systems the computer is used for data storage with no, or minimal, numerical processing.

Video storage and television display of the scintillation events as recorded from the gamma camera CRT display has been described by Ashburn et.al. (125) but such devices

have no application in digital data processing.

The Autofluoroscope of Bender and Blau (126) combined the stationary capabilities of the Anger camera with digital storage and display capabilities in one instrument. The limited resolution, small size of the field of view and inflexibility of collimator design are serious limitations of this instrument.

CHAPTER 6

EXPERIMENTAL METHODS

6.1 Patients

Patients examined were referred from the clinical services of the University Hospital, the Edmonton General Hospital, the Misericordia Hospital, the Royal Alexandra Hospital, the Charles Camsell Hospital, the Dr. W.W. Cross Cancer Institute, and from the private offices of several physicians. The patients were being investigated for various clinical disorders including abdominal pain of uncertain origin, thrombophlebitis, depression, diarrhea, metastatic disease of unknown primary origin, hypoglycemia, pancreatitis and pancreatic neoplasm.

The patients were allowed to eat normal meals (if possible) and an interval of approximately two hours was generally allowed between the last meal and the scan procedure. Approximately one half hour prior to the time of scanning the patient drank one or two glasses of milk. A review of suggested patient preparation protocols (Chapter 3) strongly suggested that any further preparation would not increase diagnostic yield in the scan procedure.

Patients were placed in the supine position beneath the gamma camera detector head, the surface of which was placed firmly against the abdomen with the center of the crystal positioned approximately one or two inches medial to the intersection of the left midclavicular line and the

left costal margin. The camera head was generally tilted five to ten degrees in the cephalad direction to fit the contour of the abdomen and to aid separation of the pancreas from the liver image by 'looking under' the liver edge. This configuration of detector and patient produced a slightly different appearance from the straight anterior scan usually obtained with rectilinear scanners.

6.2 Radioisotopes

Initially 198-Gold colloid was used to obtain the liver image. 100-150 microCuries were administered intravenously. This material presented several problems:

1. significant radiation dose to the liver, spleen and bone marrow,
2. the relatively high energy of the 412 KeV major gamma emission of 198-Gold is difficult to collimate and there is resultant loss of image resolution,
3. there is a low efficiency of detection of this photon energy in the Anger type gamma camera,
4. it was frequently found that previously administered 131-Iodine labelled Rose Bengal for liver scanning studies resulted in artefactual contribution to the 198-Gold scan. These artefacts were seen as radioactivity in the small and large bowel and were the result of inclusion of the high energy gamma-rays of 131-Iodine in

the 198-Gold energy discriminator 'window'.

When 99m-Technetium sulfur colloid became available for liver scanning this material was substituted for 198-Gold colloid with the following advantages:

1. reduced radiation dose to the patient,
2. readily available radioisotope of high specific activity,
3. good photon energy for collimation and inccreased image definition,
4. high efficiency of detection in the Anger type gamma camera,
5. decrease in time required for the scan,
6. more accurate patient positioning could be accomplished as the 99m-Technetium sulfur colloid liver scan could be completed before the pancreas scan,
7. the higher count rate associated with 99m-Technetium sulfur colloid gives statistically more significant data for subsequent digital subtraction.

75-Selenium-methionine was used in all studies for pancreatic visualization. The 265 and 280 KeV gamma-rays of 75-Selenium are detected with moderately good efficiency with the Anger camera. The major disadvantage of 75-Selenium-methionine is its relatively long physical and biological half lives, as discussed in Section 2.15

6.3 Equipment

A Nuclear Chicago Pho-Gamma III gamma-ray camera equipped with a high energy, parallel, multi-apperture collimator was employed in this investigation. Original scintiphotos were obtained with the gamma camera Polaroid oscilloscope camera.

The positioning signals and scintillation event signals, after discrimination and digitization, were stored in a 1600-channel multi-parameter analyzer, used in the 40 x 40 matrix mode, with the original image expanded so as to have the pancreatic image fill the matrix as completely as possible. Dual analogue-to-digital converters (ADC) were employed for digitization of the scan data. A Polaroid oscilloscope camera was used to obtain pictures of the displayed digital matrices. A data processor provided immediate summed matrix values in selected regions of interest.

A block diagram of the experimental set-up is given in Figure 6.3.1.

6.4 Scan Procedure

A) Initial procedure using 198-Gold

In the first 36 patients 200-300 μCi of 75-Selenium-methionine were injected intravenously and an initial localizing scintiphoto obtained approximately five minutes later. This time interval allowed adequate clearance of 75-Selenium-methionine from blood and accumulation in the pancreas. The patient was repositioned if necessary

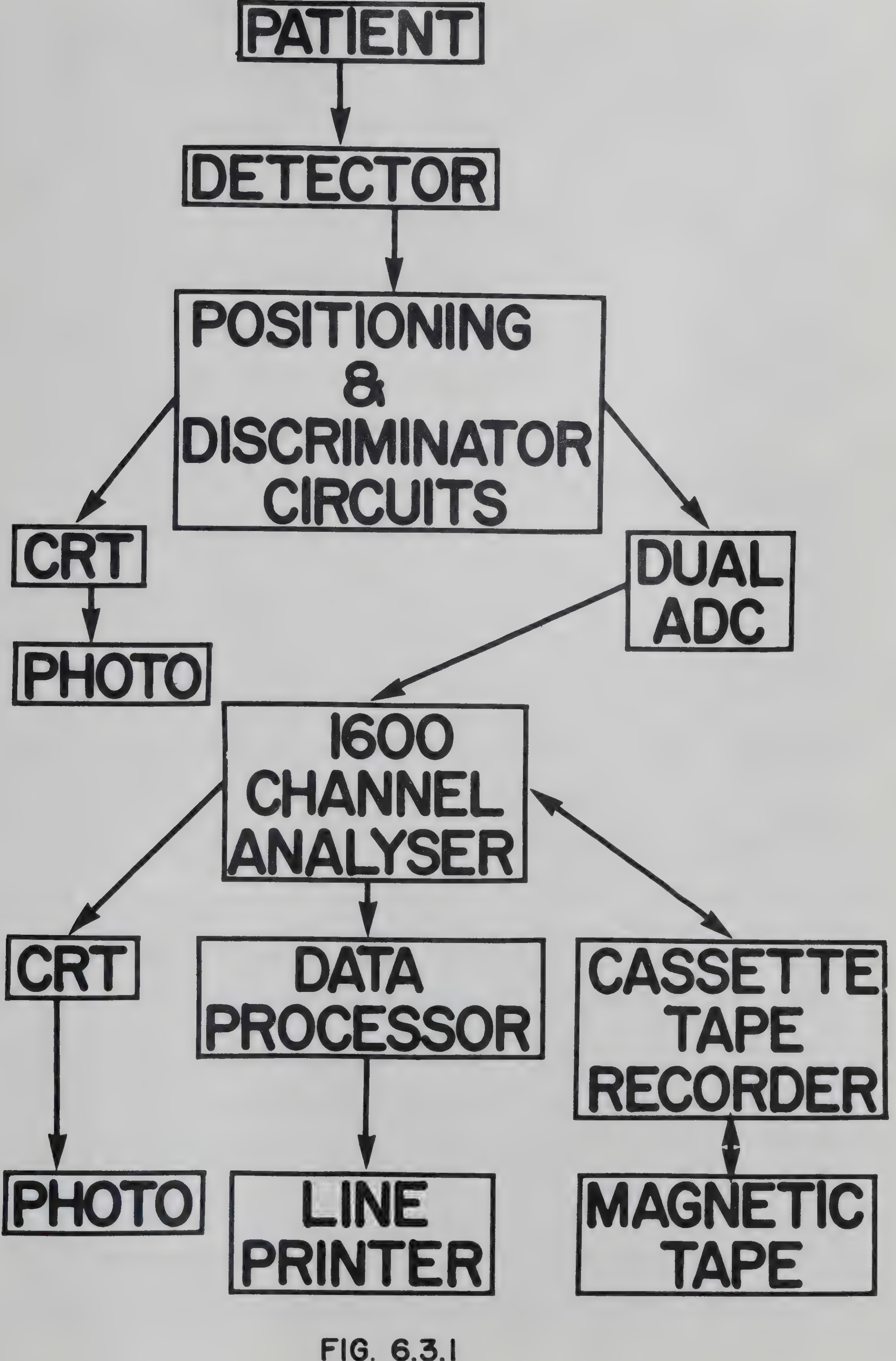

PATIENT
DETECTOR
POSITIONING & DISCRIMINATOR CIRCUITS
CRT
PHOTO
DUAL ADC
1600 CHANNEL ANALYSER
CRT
DATA PROCESSOR
CASSETTE TAPE RECORDER
PHOTO
LINE PRINTER
MAGNETIC TAPE

FIG. 6.3.1

and several scintiphotos of approximately ten minutes duration were obtained. The total counts collected for each scintiphoto ranged from 50-150 thousand counts (Figure 6.4.1a).

Despite the suggestion by several authors that scanning should be carried out one half to two hours post-injection the above procedure was selected, as a maximum tissue concentration of 75-Selenium-methionine is obtained in the pancreas in about 30 minutes (24).

The counts accumulated over approximately one half hour were stored in a 40 x 40 format in the 1600-channel magnetic core memory. Accumulation of scan data over this length of time allowed complete visualization of the pancreas with smoothing of minor regional variations in radiopharmaceutical concentration which occurred in the organ during the course of the procedure.

The data matrix was then displayed and photographed in digital form on the analyzer CRT display (Figure 6.4.1c). An area of the scan unique to the liver and well separated from pancreatic tissue was selected (Figure 6.4.1e) and numerical values for the total counts within this area obtained via data processor and fast paper tape printer (Figure 6.4.1f). The digital image was then stored on magnetic tape.

Approximately 100 µCi of 198-Gold colloid were then injected intravenously and, after a short latent period

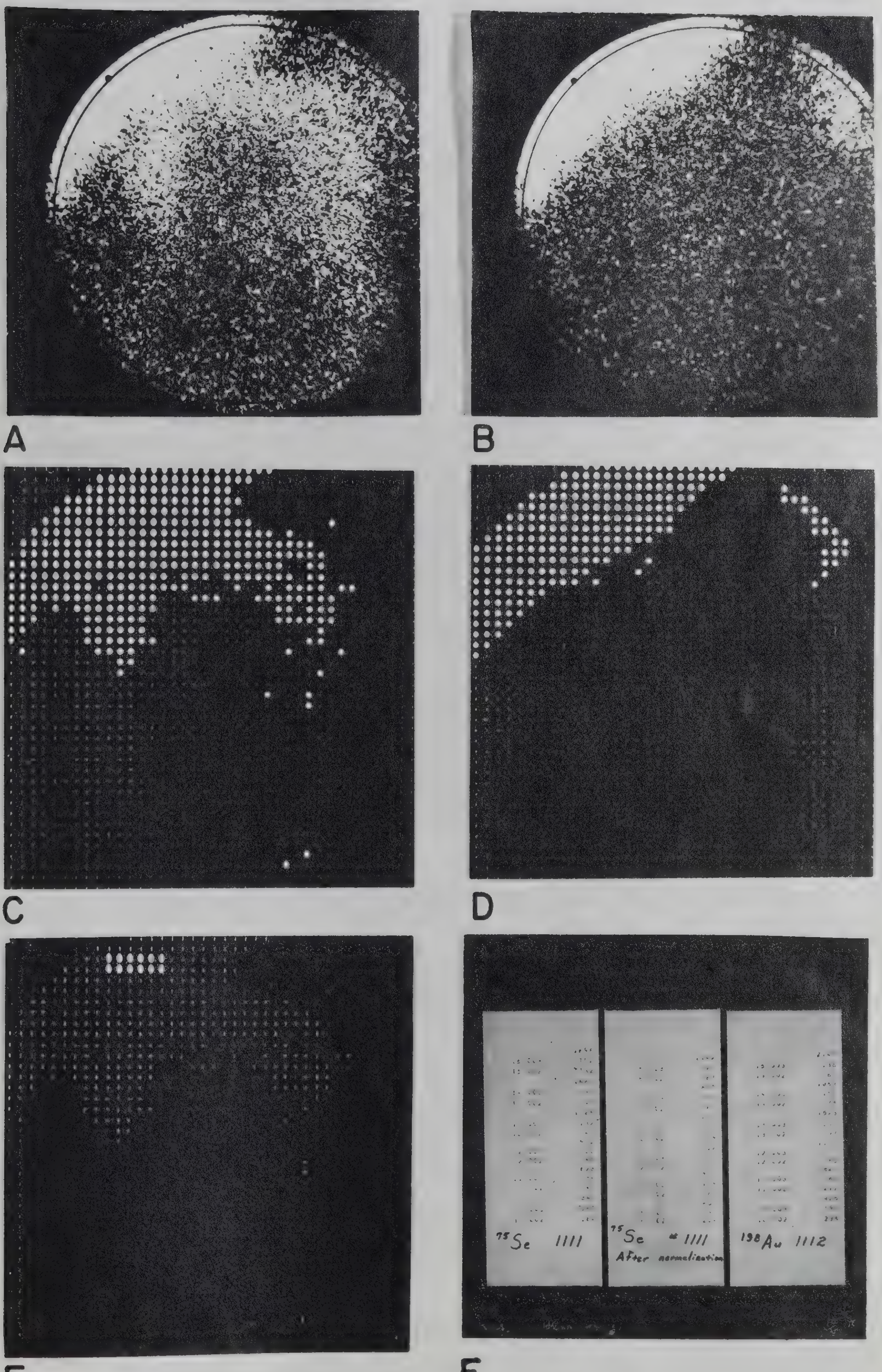


FIG. 6.4.1

to allow hepatic accumulation of the radiopharmaceutical, a scintiphoto of approximately 50 thousand counts was obtained of the liver (Figure 6.4.1b). This image was stored on magnetic tape, displayed in digital form and photographed (Figure 6.4.1d). The total counts from the previously selected region of interest were obtained via the fast paper tape printer (Figure 6.4.1f).

B) Revised procedure using 99m-Technetium

For the subsequent 210 scans, 99m-Technetium sulfur colloid was injected first, and after a short latent period, a preliminary scintiphoto was obtained. The patient was repositioned if necessary and a final scintiphoto taken (Figure 6.4.2a). The digital image was stored, displayed and photographed (Figure 6.4.2c). Total counts were again obtained from a region of interest selected to represent liver activity.

75-Selenium-methionine was then injected, scintiphotos obtained and the image processed in a manner identical to that described in 6.4A .

A 20 or 25% discriminator window was set for the 412 KeV gamma-ray of 198-Gold colloid, the 140 KeV gamma-ray of 99m-Technetium or the 265 and 280 KeV gamma-rays of 75-Selenium (127) as required.

6.5 Immediate Subtraction

The total counts within the region of interest

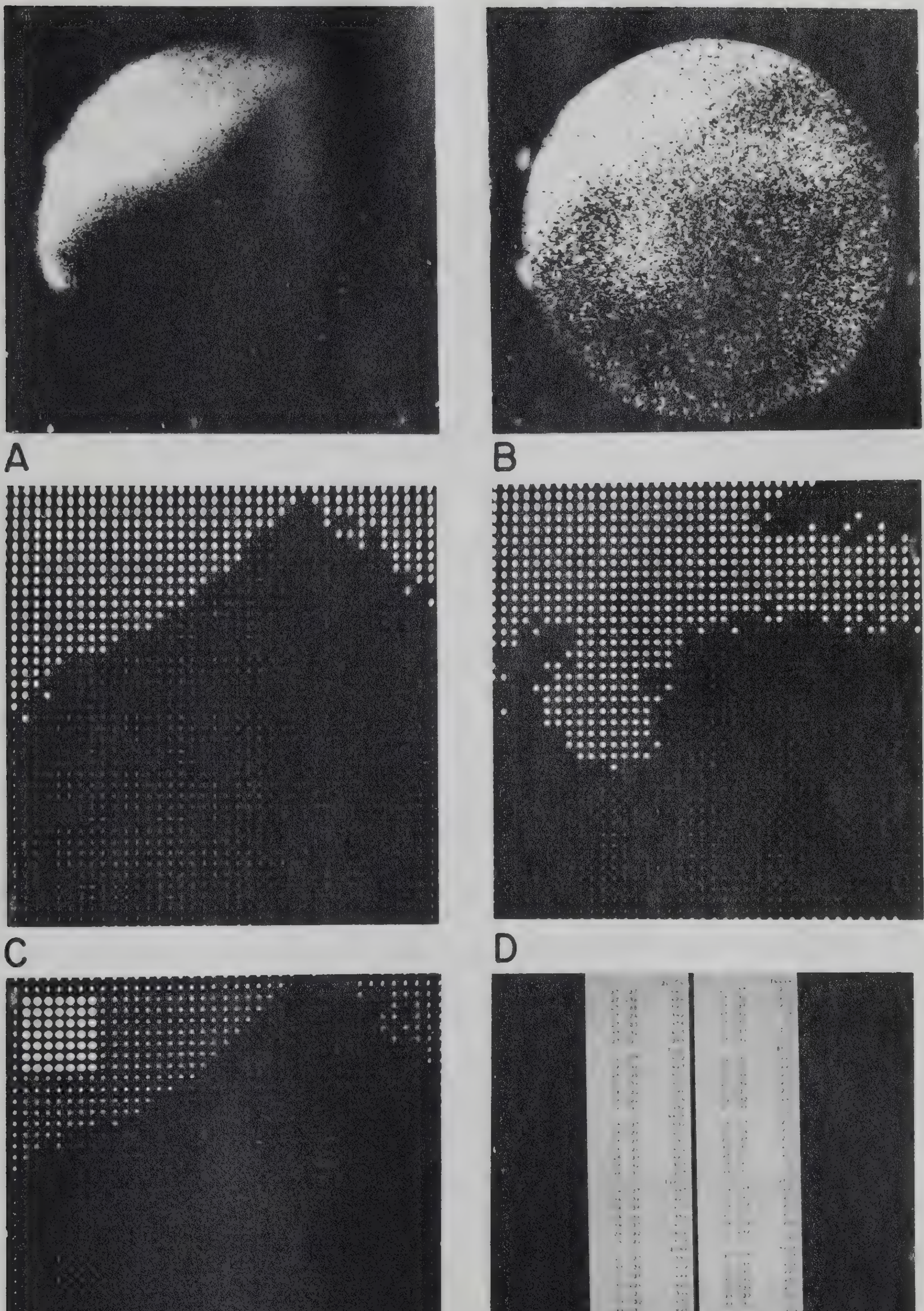


FIG. 6.4.2

ROI), which had been obtained from the data processor and paper tape printer for both scans, were used to calculate a total count ratio of gold to selenium or technetium to selenium for an area unique to the liver. The selenium matrix was 'normalized' to match the radio-colloid matrix in the ROI by multiplying the selenium matrix by the radio-colloid to selenium ratio. The effect of this multiplication was not only to normalize the ROI but as the ROI represented liver counts generally to normalize the count rate values for every point in the liver. Multiplication was performed by storing the selenium matrix the required number of times as indicated by the radio-colloid to selenium ratio (Figure 6.5.1). The selenium matrix was stored in the 1600-channel analyzer in positive form and the colloid (198-Gold or 99m-Technetium sulfur colloid) matrix in negative form. The effect of this procedure was to subtract the colloid (liver) matrix from the selenium (liver and pancreas) matrix leaving the pancreas image (the difference image).

Due to slight variations in the ratio values in individual matrix positions negative numbers occurred at some points in the liver (Figure 6.5.2a). These were expressed (due to the inherent design of the analyzer) as large positive numbers (Figure 6.5.2b). These numbers were eliminated by adding a uniform positive 'test' signal into all matrix positions until all points returned to

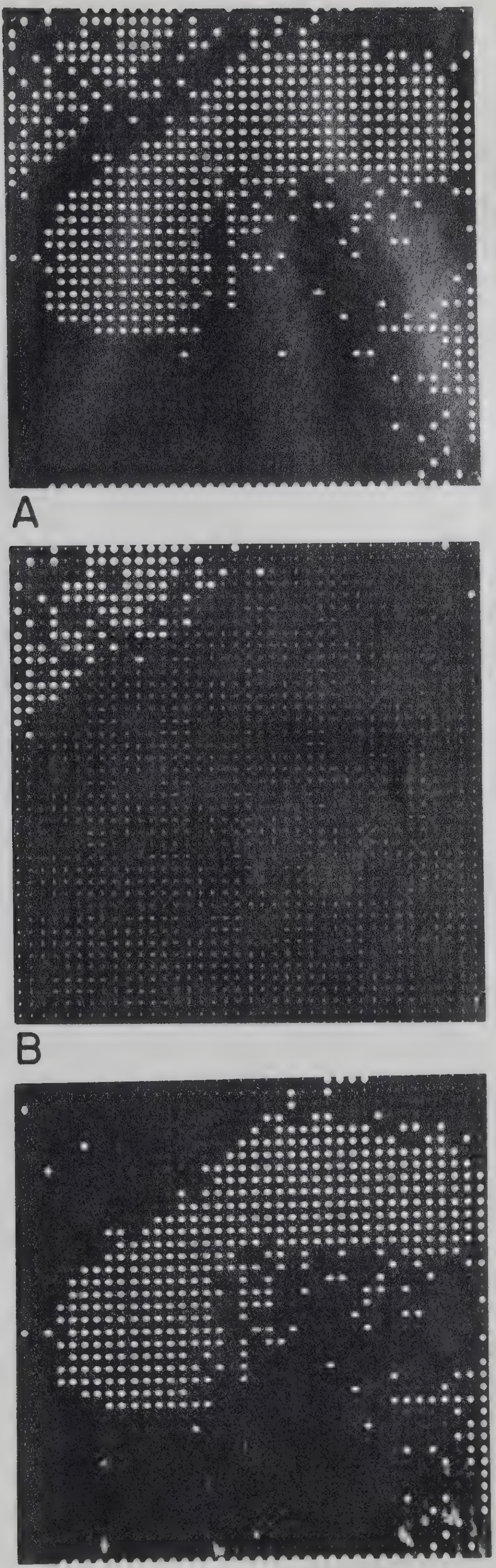


FIG. 6.5.2

small positive values (Figure 6.5.2c).

The resulting image is representative not only of the pancreas but also of some contribution from the small bowel, kidney, muscle, bladder and blood (Chapter 7).

6.6 Computer Processing

The two scan images for a particular patient, initially stored on magnetic tape cassettes, were transferred to computer compatible magnetic tape with a numeric identifier for each matrix. A computer program was written for processing of these data on an I.B.M. 360/67 computer available on the University of Alberta Campus. A flow diagram of the computer program is shown in Figure 6.6.1.

To initiate scan processing, the scan data for a given patient were selected via the remote terminal facility by the numeric identifier, and read into core. Anomalous points ('noise') were eliminated by a fixed point averaging technique . Data smoothing based upon a variable spatial averaging method (117) was performed for each point. Coordinates of the ROI selected at the time of the initial 'immediate subtraction' were then supplied to the computer program either via the remote terminal facility, or via a punched card reader, and total count ratios of the ROI obtained. Normalization and subtraction of the scan data were then performed.

To estimate the validity of the computer processed scan, symbolic density plots of the difference

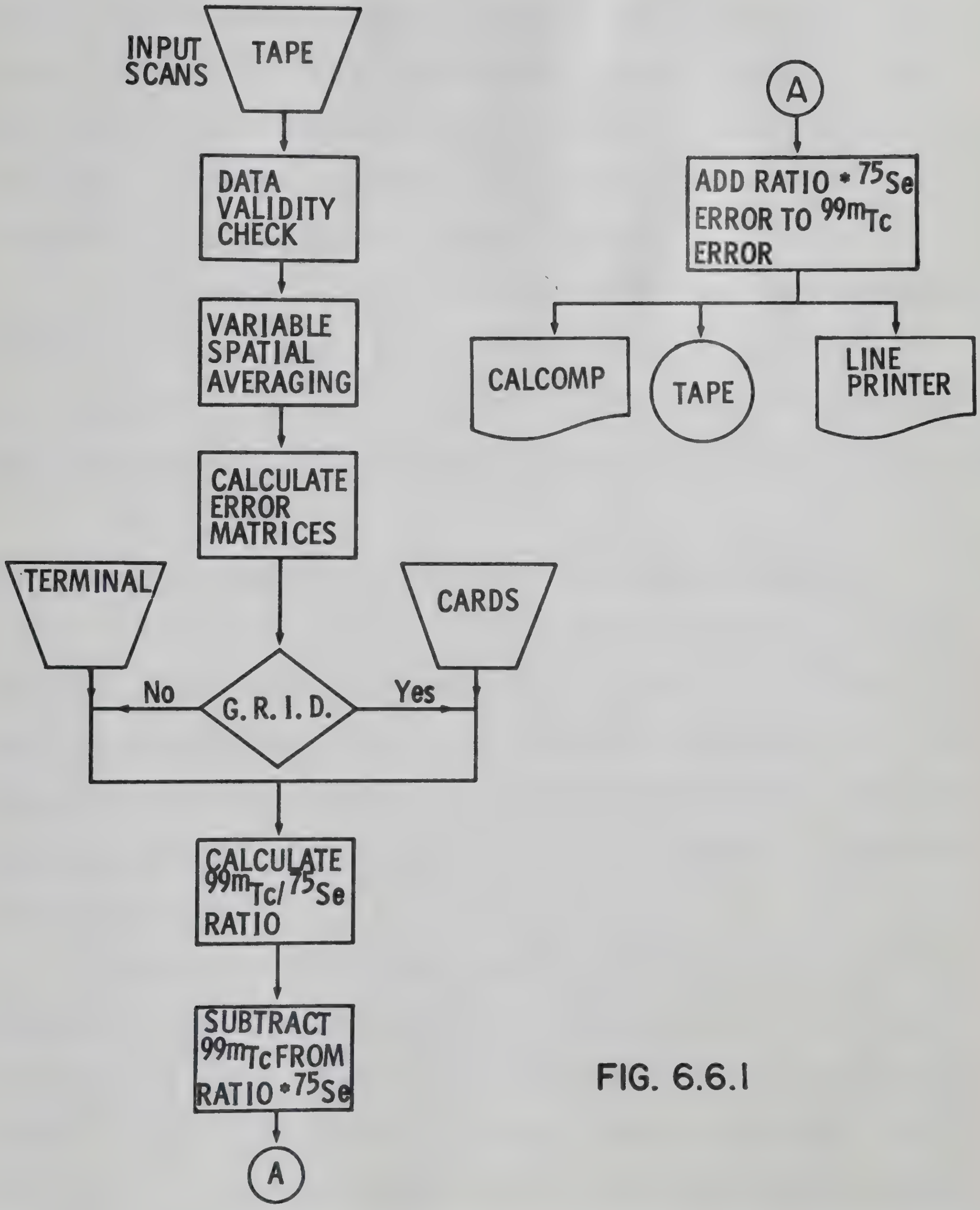

INPUT SCANS
TAPE
DATA VALIDITY CHECK
VARIABLE SPATIAL AVERAGING
CALCULATE ERROR MATRICES
TERMINAL
CARDS
No
G.R.I.D.
Yes
CALCULATE $^{99m}Tc/^{75}Se$ RATIO
SUBTRACT ^{99m}Tc FROM RATIO * ^{75}Se
A
A
ADD RATIO * ^{75}Se ERROR TO ^{99m}Tc ERROR
CALCOMP
TAPE
LINE PRINTER

FIG. 6.6.1

image with various levels of 'background erase' were obtained. This effect was achieved by successive subtraction of one and two experimental standard deviations (σ) from the difference image. The resulting matrices were printed on the line printer with suppression of negative numbers. Points surviving as positive numbers following this procedure possessed a high degree of significance.

Following subtraction, the difference image and the difference image minus 1σ and 2σ were stored on magnetic tape and several methods for their presentation were studied. These techniques are illustrated and described in Section 6.8.

6.7 Graphical Remote Interactive Display (GRID)

During the course of this investigation an inter-reactive graphics device connected on-line to the 360/67 computer became available. The data for each scan could be displayed on a CRT monitor and boundary definition using a light pen performed for presentation of regions of interest to the computer.

With the exisiting computer operating system the graphics device was not truly inter-reactive in the sense of providing the boundaries to the subtraction program with receipt of the resultant difference image immediately on the CRT display. The boundaries in fact were punched on cards and presented to the computer program as a separate procedure.

A variable grey brightness scale was selected for

optimum count rate representation and interpretation as shown in Figure 6.7.1.

At a later date, when the device is truly inter-reactive, the scan data can be stored from magnetic tape into core. The scan data will be displayed, region of interest boundaries selected, the boundaries presented to the computer program, data reduction and subtraction carried out and the difference image presented immediately on the graphics display screen.

An evaluation of the influence of differing boundary definitions upon subtracted image was made with GRID by defining several boundaries for one particular image and comparing the resultant difference images from the use of each of these boundaries for total count ratio averaging. The results of this procedure are shown in Figure 6.7.1 where three subtracted images are presented for three different boundary conditions. As can be seen, the selection of boundaries, if properly located, has little influence on the final difference image. This is to be expected as the total count rate ratios in the selected areas of the liver are very similar.

6.8 Data Presentation

Original scintiphotos of the radio-colloid (liver) scan and the 75-Selenium-methionine (liver and pancreas) scan are illustrated in Figure 6.8.1a and 6.8.1b. These were obtained from the CRT display incorporated in the control console of the gamma camera.

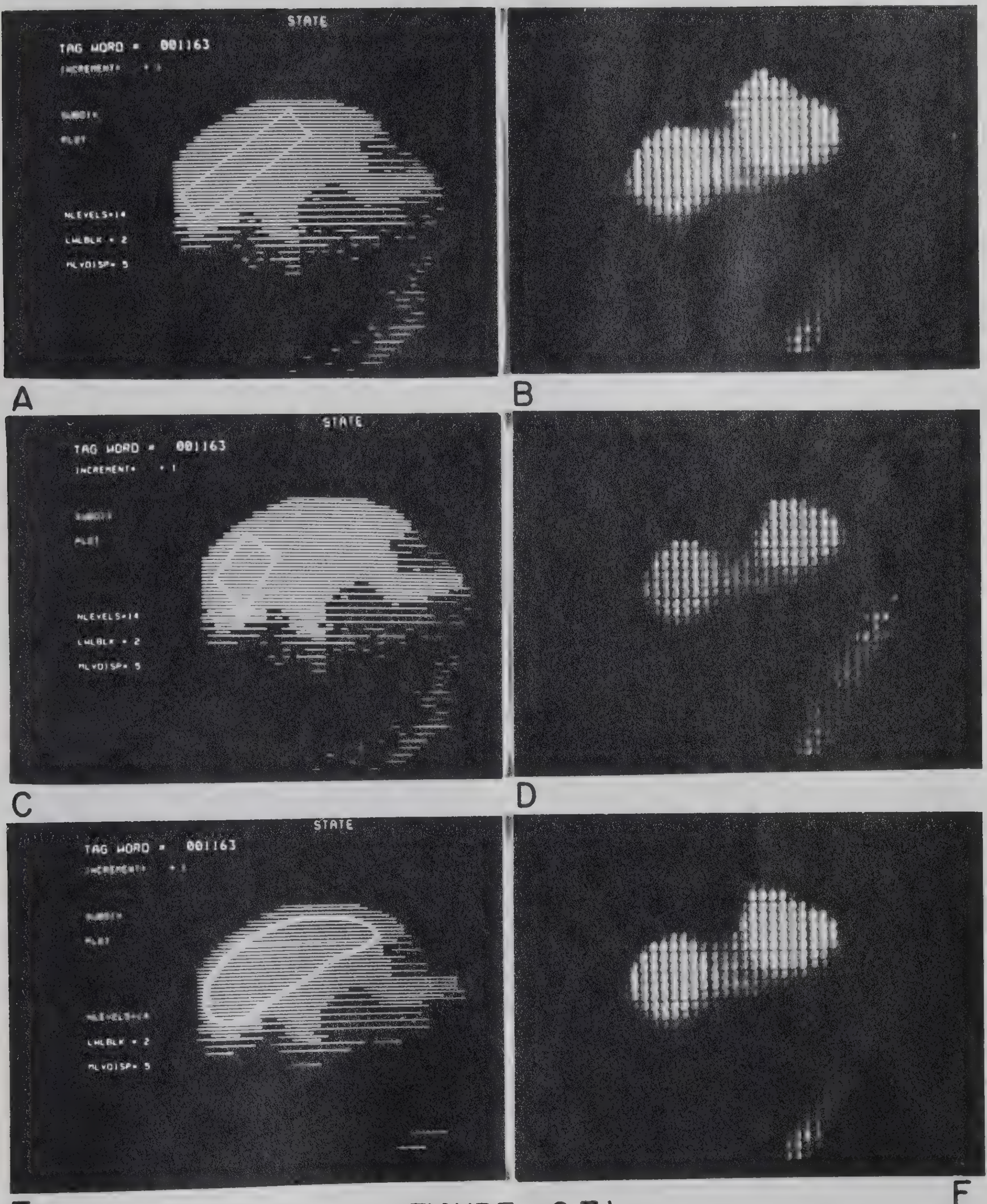

STATE
TAG WORD = 001163
PLOT
NLEVELS=14
LWLBLK = 2
NLVDISP= 5
A
B
STATE
TAG WORD = 001163
INCREMENT= + 1
PLOT
NLEVELS=14
LWLBLK = 2
NLVDISP= 5
C
D
STATE
TAG WORD = 001163
PLOT
LWLBLK = 2
NLVDISP= 5
E
F

FIGURE : 6.7.1

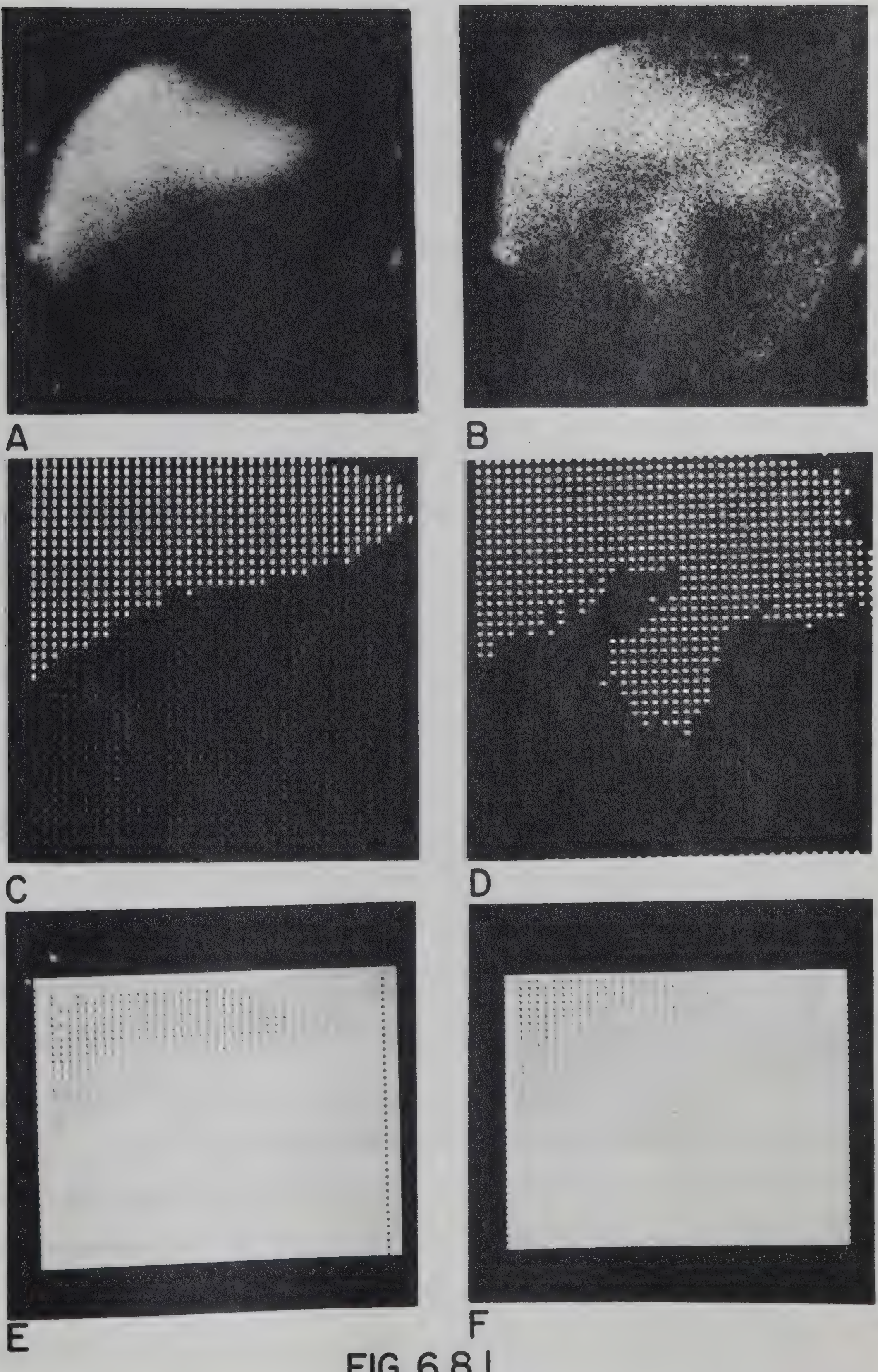


FIG. 6.8.1

(There is an inherent limitation of dynamic range in Polaroid film which can be avoided by the use of high contrast photographic film, but the convenience, sensitivity, rapid development and ready availability of the Polaroid film partially, if not completely, outweighs this drawback). In about 50% of cases, diagnostic images were obtained in these scintiphotos.

Following digitization and storage of scan data, the scan matrix was displayed on the CRT of the 1600-channel analyzer and this image also photographed with Polaroid film as illustrated in Figure 6.8.1c and 6.8.1d.

Figure 6.8.1e and 6.8.1f are symbolic density plots of the same data after smoothing using 9 symbols to give increasing density for increasing count rates. Only the 4th to 9th levels are used in this illustration producing a degree of 'background erase'.

The difference image obtained by subtracting the radio-colloid matrix from the normalized 75-Selenium-methionine matrix is illustrated in Figure 6.8.2a. The difference image minus 1σ and minus 2σ are illustrated in Figure 6.8.2b and c.

The difference image matrix stored on magnetic tape was played back into the 1600-channel analyzer and photographed on Polaroid film giving an image as illustrated in Figure 6.8.3. Figure 6.8.3a, b and c shows a CRT display with only one level of light intensity. The data threshold level in effect provided a single isocount contour

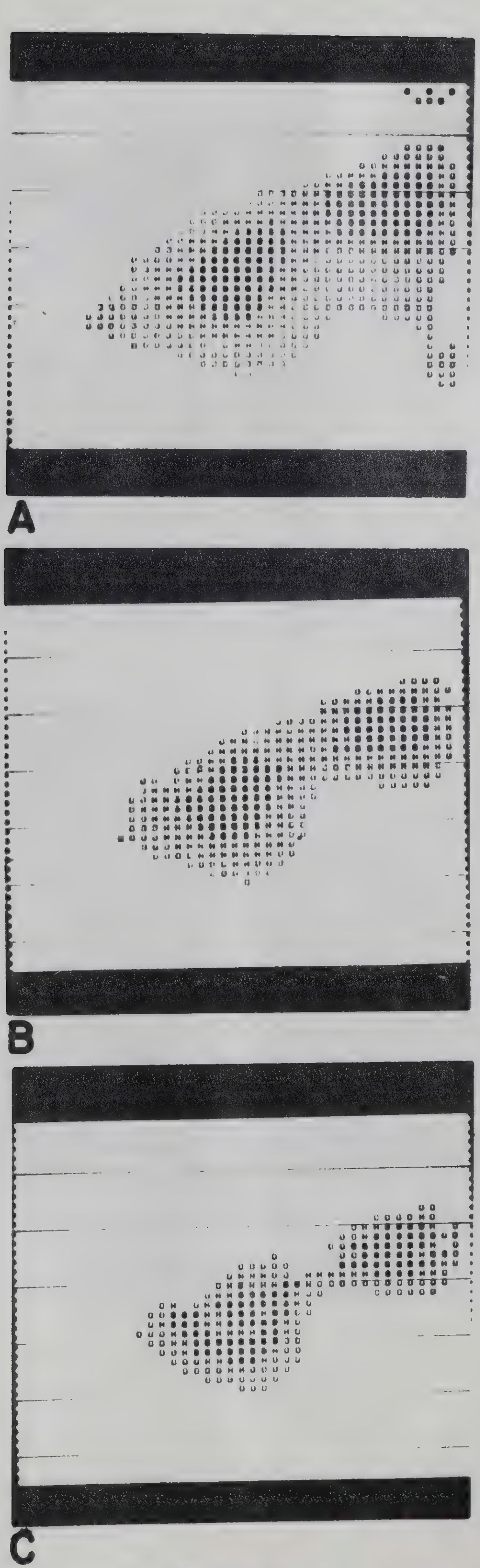


FIG. 6.8.2

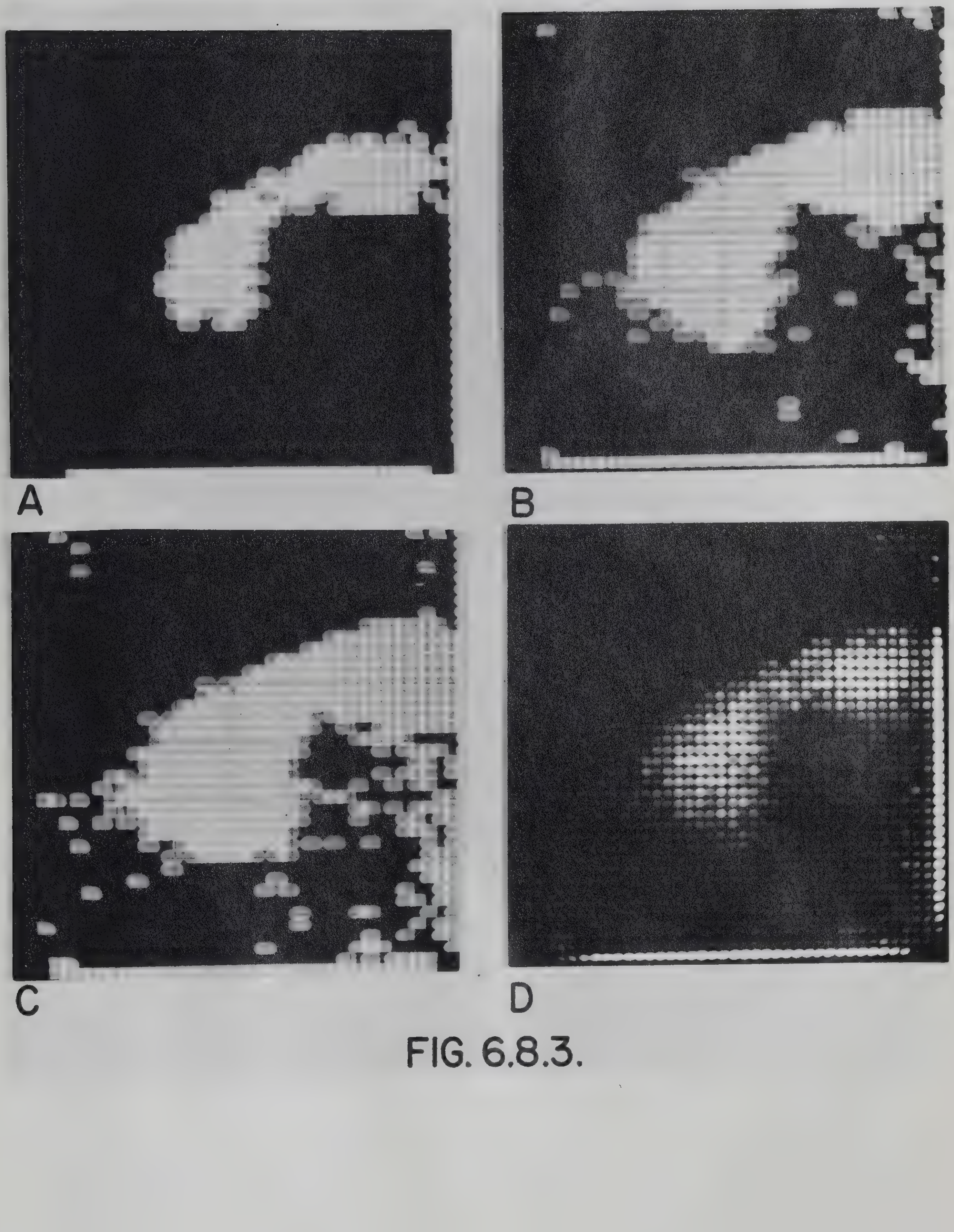


FIG. 6.8.3.

which could be varied to give an impression to the viewer of a continuously variable, multi-iscount contour. Photographic representation of these continuous levels is impossible but three single levels are represented. Figure 6.8.3d shows the same matrix with a nine grey scale which represents varying count rates as different light intensities. This, in effect, gives nine isocount contours. Careful selection of data threshhold and range of the grey scale gives enhanced contrast in areas of low count rate difference.

The stored difference image matrix can also be used to obtain a contour plot with a Calcomp plotter when this facility becomes available.

CHAPTER 7

THE APPEARANCE OF THE NORMAL AND ABNORMAL PANCREAS SCAN

7.1 Normal

Normal pancreatic morphology as demonstrated by pancreas scanning with 75-Selenium-methionine has been reviewed by King et.al., (77) Kakehi et.al. (78) and Riccobono (128).

The normal pancreas shows a fairly regular contour in one of several organ configurations. As demonstrated by the method described in this thesis, the pancreas most often appears as 'sigma' or 'pistol' shape (Figure 7.1.1). This is probably due to a combination of the angulation of the camera head and visualization of the pancreas as it 'droops' over the vertebral column.

Uniform distribution of radioisotope throughout the pancreatic parenchyma is seen in some cases but the majority of cases show a vertical, linear area of decreased, or essentially absent, radioisotope concentration in the body of the pancreas where the organ overlies the aorta and vertebral column in the midline. Concentration of radioisotope in the tail is sometimes higher, raising the possibility of a physiological obstruction in the midline. Powell (95) has pointed out that changes in radioisotope concentration are frequently seen in different portions of the pancreas as a function of time. This has not been a striking finding in the present investigation and there

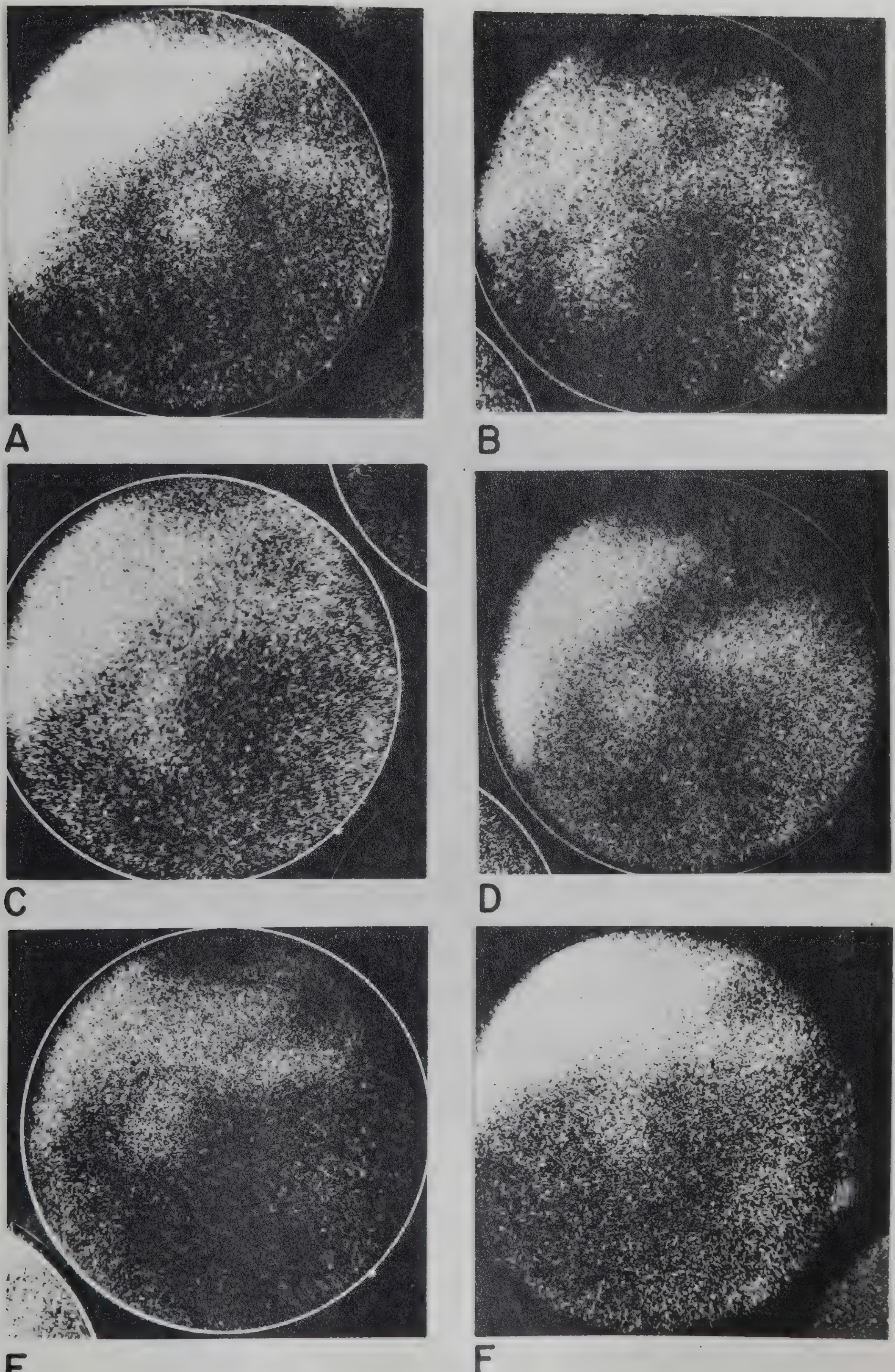


FIG. 7.1.1

is a strong possibility that this phenomenon, in rectilinear scanning, may in fact be due to slight variations in the position of the pancreas due to patient movement. King et.al. (77) have suggested that changing pancreatic morphology may be due to peristalsis and, although nobody has disproven this argument, I would suggest that the likelihood of such peristalsis causing gross morphologic changes is rather remote.

The size of the pancreas varies within wide limits and is not generally an indication of the presence or absence of pancreatic disease.

The body of the pancreas generally lies immediately adjacent and nearly parallel to the inferior margin of the liver. The liver is usually quite well defined in the 75-Selenium-methionine scan although not of sufficient quality for routine liver scanning.

Radioactivity in the left flank is almost invariably seen and is due to renal accumulation of radiopharmaceutical with superimposed small bowel (most likely jejunal loop), spleen and abdominal musculature (60). Radioactivity in the small bowel is probably due to pancreatic enzymes and succous entericus.

Activity in the right flank is usually not seen as this is excluded from the field of view by positioning of the detector head.

Duodenal activity (129) is significant and it has

been demonstrated in animal experiments that pancreatic: duodenal activity on a unit weight basis is possibly only 2:1 although the ratio of extraction efficiencies is probably about 4:1 for the two tissues. The pancreatic head is therefore surrounded by considerable activity in the duodenal mucosa and this undoubtedly contributes to the apparent size of the head of the pancreas as seen in some scans.

There will be blood-borne activity of 75-Selenium-methionine, both as the original radiopharmaceutical and as circulating blood proteins, which will contribute to background activity in the abdomen.

Partial pancreatectomy will usually show normal uptake in remnant pancreas when this remnant is free of disease. An example of this is illustrated in Figure 7.1.2.

7.2 Abnormal

The presence of pancreatic neoplasm generally results in an area of reduced radioisotope concentration in the involved area (Figure 7.2.1). Frequently, complete absence of radioisotope concentration in the entire pancreas is seen, where obstruction, secondary inflammation and parenchymatous destruction is present (Figure 7.2.2).

Functional tumours of the pancreas have been reported as showing increased, rather than decreased, concentration of radioisotope (49,50) but I have not been

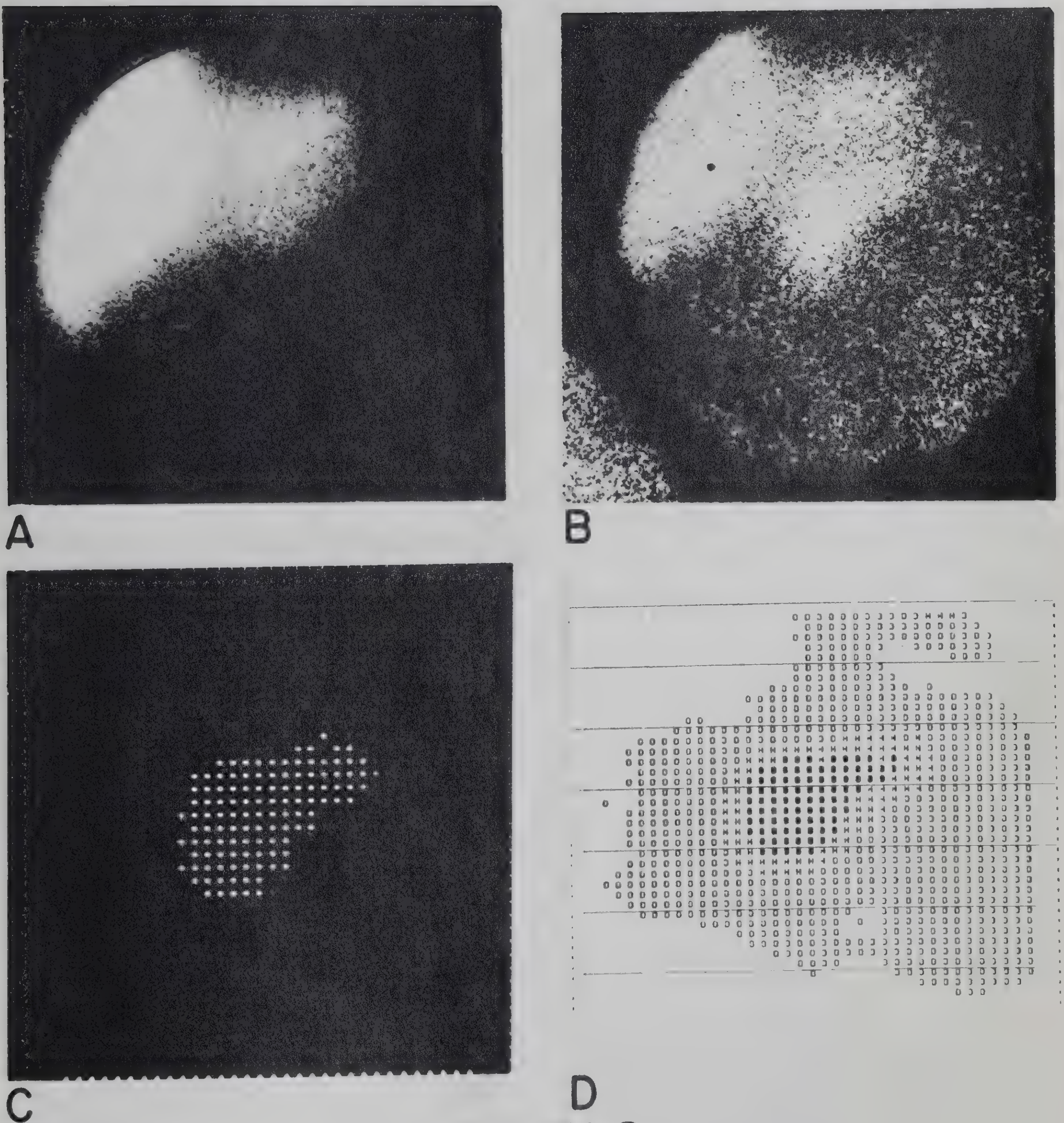


FIG. 7.1.2

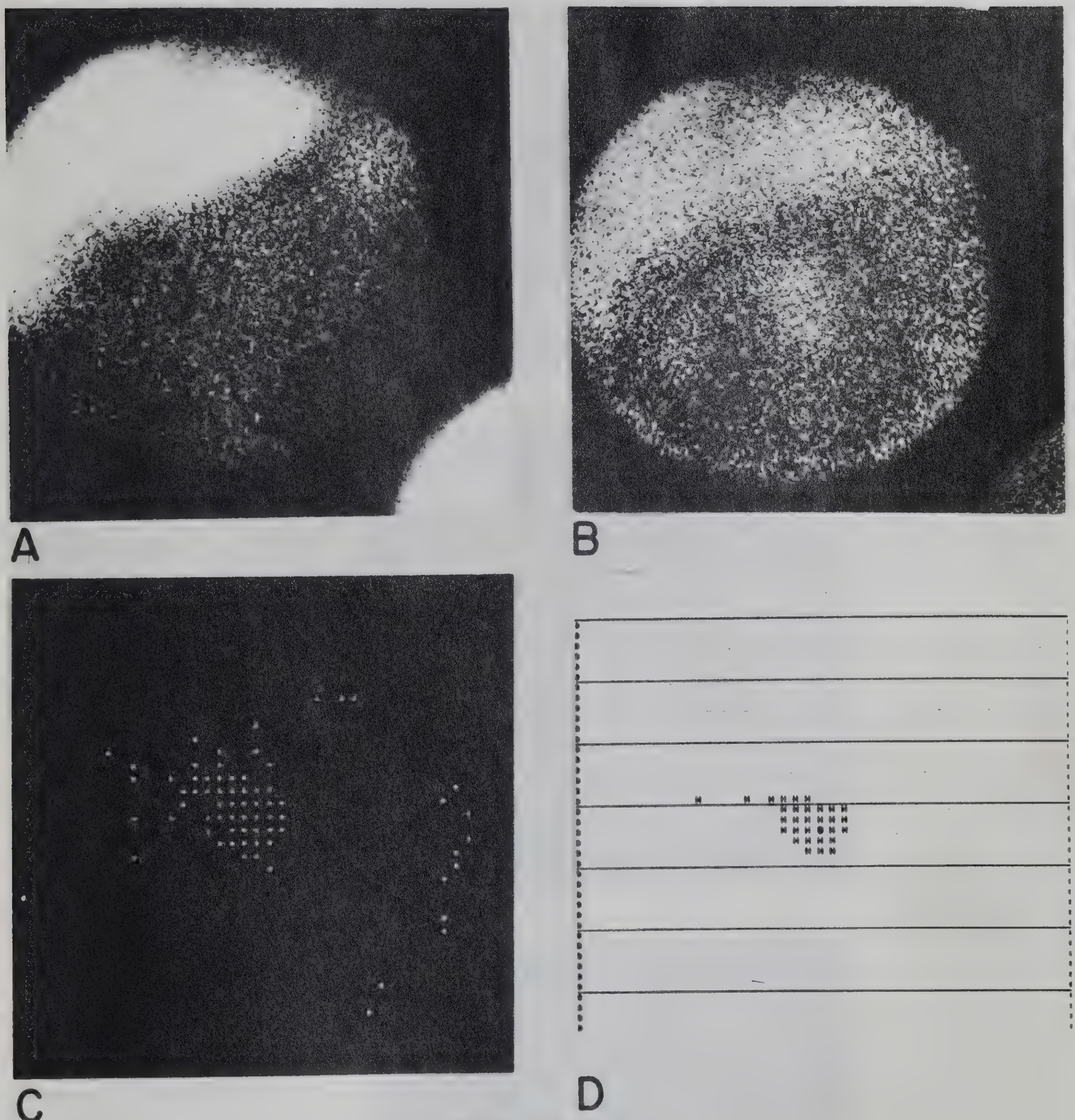


FIG. 7.2.1

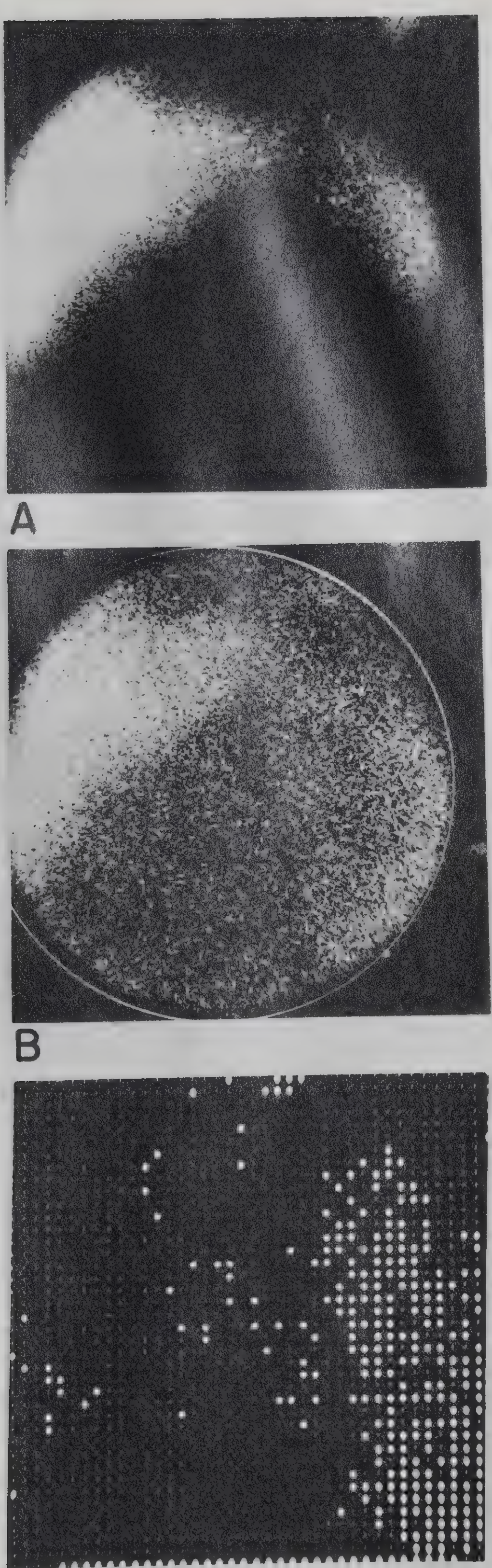


FIG. 7.2.2

able to demonstrate a well defined area of increased uptake in any of several cases of insulinomata or Beta cell hyperplasia examined. No proven cases of Zollinger-Ellison syndrome have been examined.

Inflammation of the pancreas usually results in decreased radioisotope concentration. Acute hemorrhagic pancreatitis invariably results in complete non-visualization in the acute phase and for several weeks thereafter (Figure 7.2.3). On the other hand mild edematous pancreatitis will sometimes show essentially normal radioisotope concentration (Figure 7.2.4). Chronic pancreatitis usually results in decreased concentration and slightly irregular distribution of radioisotope without discrete focal abnormalities. The gross pancreatic architecture is often fairly well preserved (Figure 7.2.5). Displacement of the pancreas is sometimes seen in psuedocyst formation although pancreatic morphology can also be poorly defined due to the presence of associated acute or chronic pancreatitis.

Yvergneaux and Vaernberg (130) have noted the return of function after removal of a pancreatic ductal stone where the original scan showed non-visualization. There were no examples of this phenomenon in the present study.

High background activity in the abdomen is seen in a number of inflammatory, dystrophic and func-

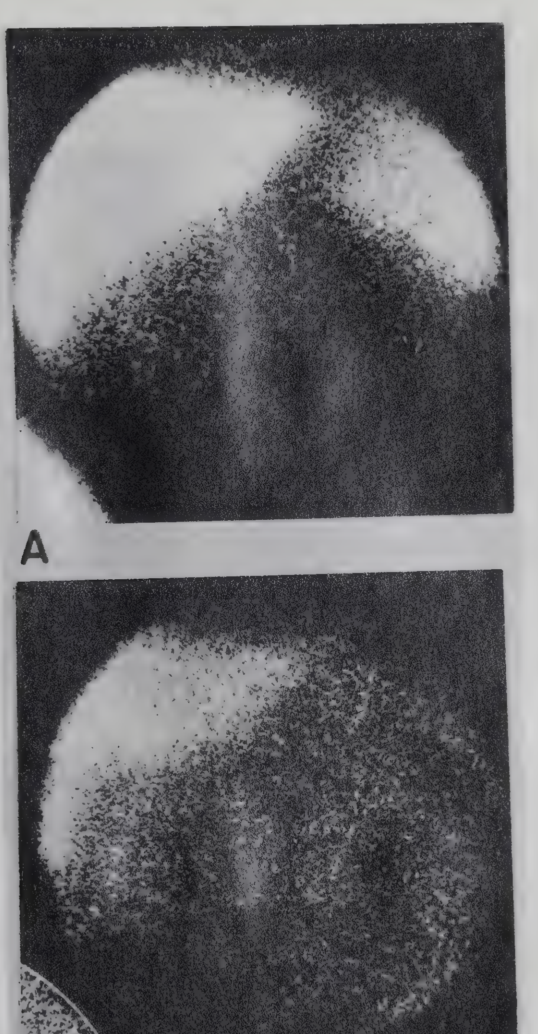


FIG. 7.2.3

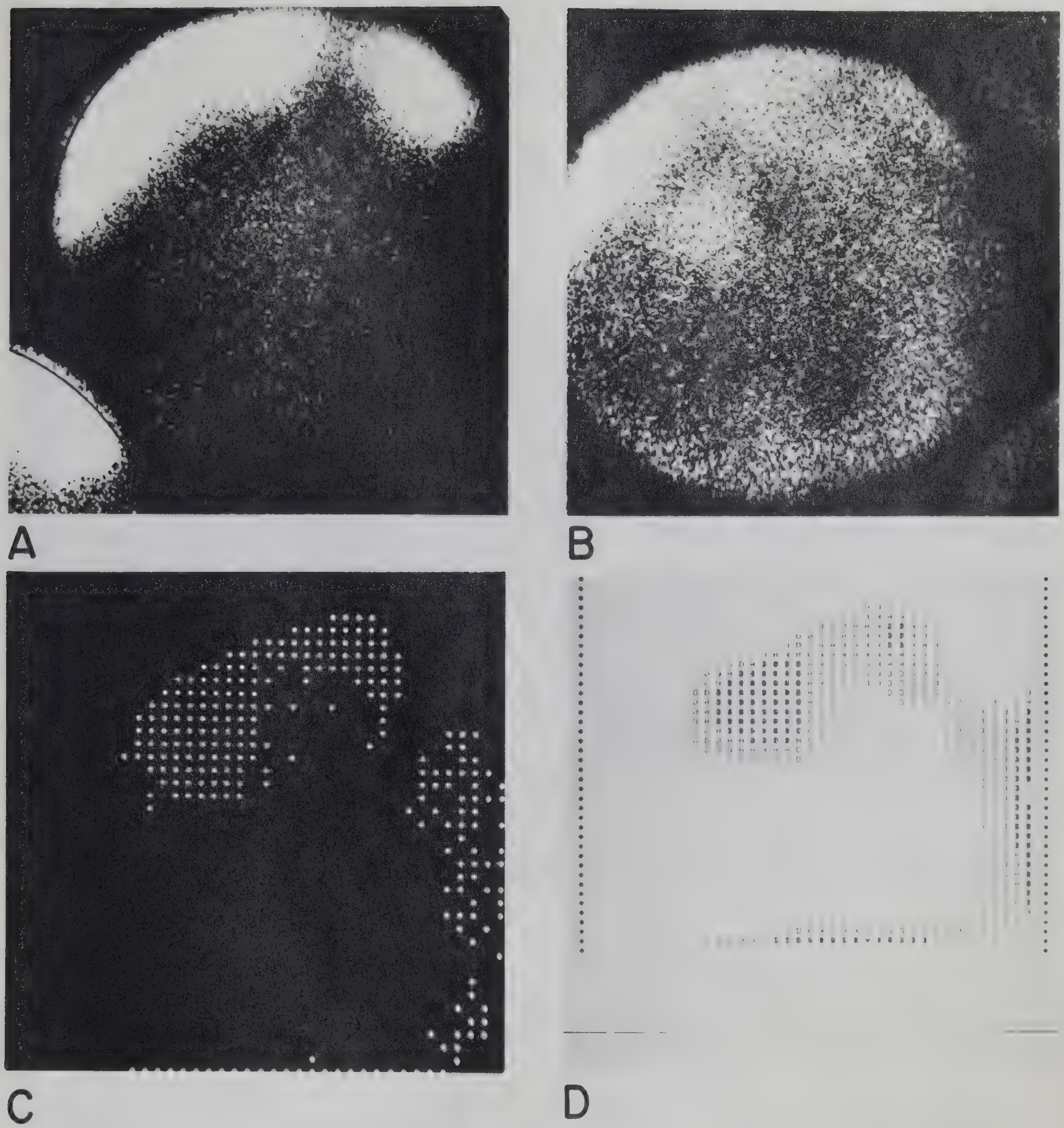


FIG. 7.2.4

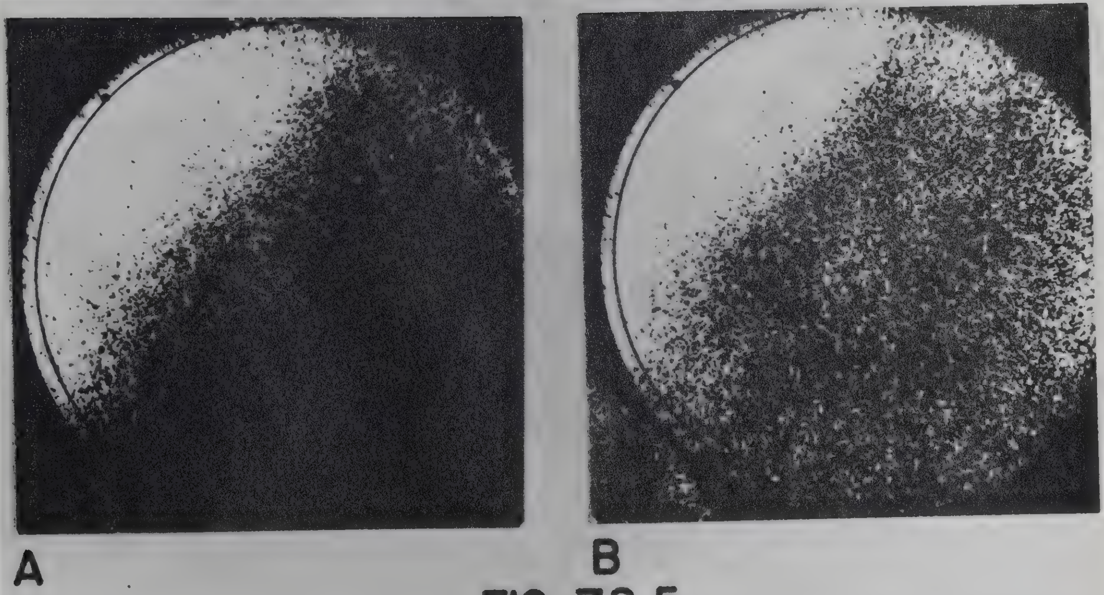


FIG. 7.2.5

tional disorders of the small bowel and probably represents excessive uptake by small bowel mucosa (Figure 7.2.6).

Previous surgery, disseminated carcinomatosis, abdominal lymphoma, stasis of gastric and small bowel content and carcinoma of the stomach tend to increase abdominal background activity (Figure 7.2.7).

Obesity of course reduces resolution and sensitivity and involuntary patient movement is occasionally a problem where considerable abdominal pain is present.

Riccobono (128) reported several cases in which the pancreas scan was abnormal shortly (less than 36 hours) after abdominal surgery although the pancreas was remote from the surgical procedure. It was also noted that the scan returned to normal several days or weeks later. The significance of this finding has not been determined.

7.3 Diabetes

Several patients examined during the course of this investigation have presented with abnormal pancreas scans but without confirmation of pancreatitis or pancreatic neoplasms.

Most of these 'false positive' scans were obtained from patients with diabetes of many years duration. The abnormality usually present was decreased radioisotope concentration of slightly irregular distribution.

The appearance was often indistinguishable from that seen in patients with chronic pancreatitis.

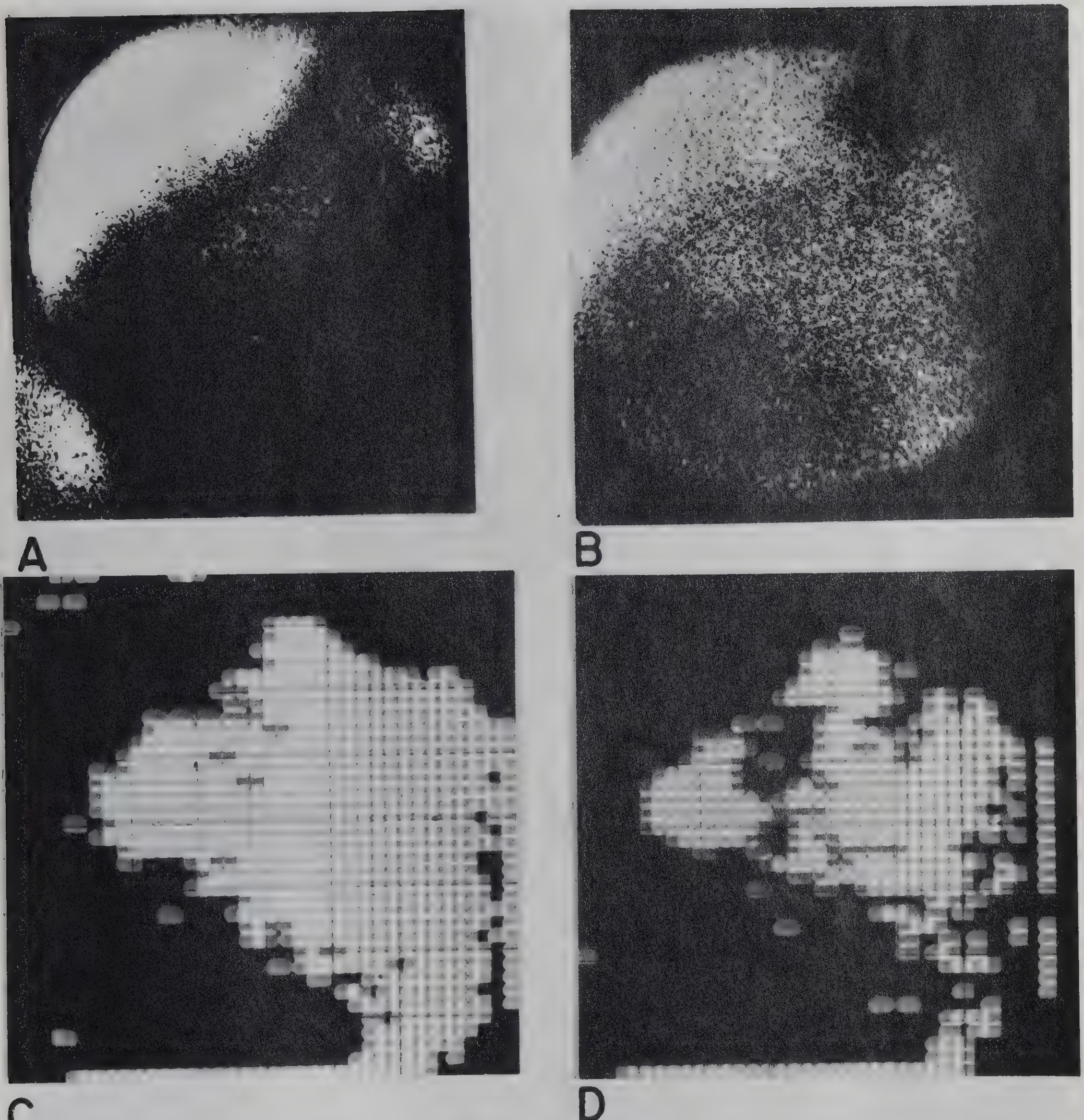


FIG. 7.2.6

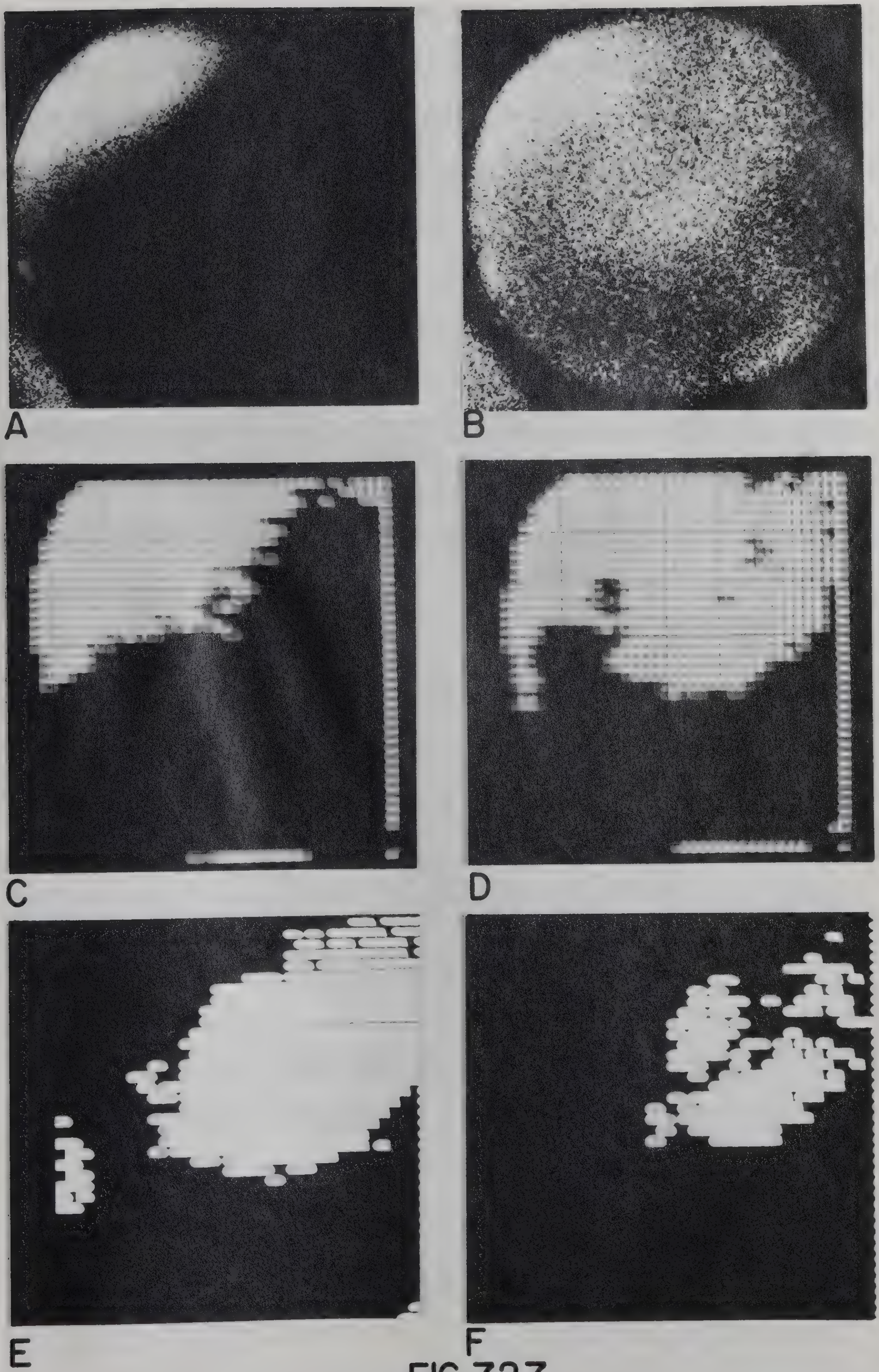


FIG. 7.2.7

It was suggested by Sodee (60) that non-visualization of the pancreas occurred frequently in patients with long standing diabetes who lacked evidence of exocrine pancreatic disease. His explanation was that ---- 'there may also be a low grade pancreatitis with infiltration of the pancreatic tissue by a mucopolysaccharide related to the disease' in these patients.

Unfortunately none of the patients in the present series who exhibited this type of abnormality have had pancreatic biopsy at surgery or post mortem. The true cause therefore remains obscure but several possible explanations should be considered;

a) that diabetes was present as an incidental pre-exisiting condition and early, undetected disease of the exocrine pancreas was also present - possibly asymptomatic and without relation to the presenting symptoms or signs which prompted the investigation.

b) that pancreatic changes associated with diabetes depressed exocrine function to the degree that uptake of 75-Selenium-methionine is also depressed i.e. that exocrine pancreatic disease was a result of the diabetes.

c) that sub-clinical exocrine pancreatic disease (e.g. previous pancreatitis or chronic pancreatitis) caused extensive destruction and/or replacement of pancreatic parenchyma. Diabetes might therefore have developed as a result of endocrine pancreatic insufficiency related to chronic and extensive pancreatic parenchymatous disease.

The abnormalities encountered in pancreas scans performed on patients with diabetes will be further discussed in Chapter 8.

7.4 Liver Disease

The radio-colloid liver scan obtained in conjunction with the pancreas scan may reveal evidence of cirrhosis, biliary obstruction, hepatic metastases, widening of the porta hepatis or hepatic displacement, as a result of pancreatic disease.

7.5 The Difference Image

It was assumed for purposes of this study that the uptake of radio-colloid per unit Kupfer cell was uniform throughout hepatic parenchyma. A similar assumption was made for the concentration of 75-Selenium-methionine in polygonal cells.

The ratio of Kupfer cell mass to polygonal cell

mass was also assumed to have uniform value.

Following stabilization of hepatic uptake of both the colloidal material and 75-Selenium-methionine, a fixed ratio therefore should exist between the two materials for a limited period of time.

The radioactivity detected by the gamma camera bears a direct relationship to the amount of radioisotope present in the liver. This relationship is not exactly the same for the two radioisotopes, as differential self-absorption and absorption by interspersed soft tissue of the abdomen will vary the amount of radioactivity detected for similar amounts of radioactivity present, where differing photon energies are concerned. More absorption of the low energy 140 KeV 99m-Technetium radiation will occur as compared to the 265-280 KeV radiation of the 75-Selenium-methionine. The relationship of radioactivity present to radioactivity detected is, however, similar for the two photon energies and was assumed to be the same for purposes of this investigation. This assumption results in slightly differing count rate profiles of the liver and thus, in some distortion of the difference image where a fixed ratio is assumed for the entire count rate surface of the two matrices. Fortunately only a slight degree of background cut-off will eliminate this distortion.

Where normal liver physiology has been disturbed, e.g. by cirrhotic or neoplastic (primary or secondary) the fixed ratio of radio-colloid to 75-Selenium-methionine

will be disturbed also. Usually some 75-Selenium-methionine will accumulate in metastatic tissue without significant uptake of radio-colloid. This will present as a positive area in the subtraction scan due to the presence of a higher selenium to colloid ratio in that area (Figure 7.5.1). Apparent distortion of the pancreas might be suggested if the artefact is adjacent to the pancreas image.

In cirrhosis it is probable that more radio-colloid will accumulate in areas of severe nodular involvement producing negative areas in the difference image. However, this does not present a problem as negative numbers are eliminated in the subtraction procedure.

Colloidal material is also accumulated by the spleen and bone marrow but fortunately this accumulation will be effectively eliminated without significant distortion of the difference image. The exception to this general rule is encountered when splenomegaly exists which obscures the tail of the pancreas. In this event, the subtraction will result in apparent localized disease of the tail of the pancreas. Splenic size must threfore be evaluated in the radio-colloid scan. The previous administration of radioactive materials for diagnostic or therapeutic purposes will result in various types of artefacts dependent upon the characteristics of the radioactive material used. The most frequent problem of this type was observed when 131-Iodine labelled Rose Bengal had been administered for conventional liver scanning.

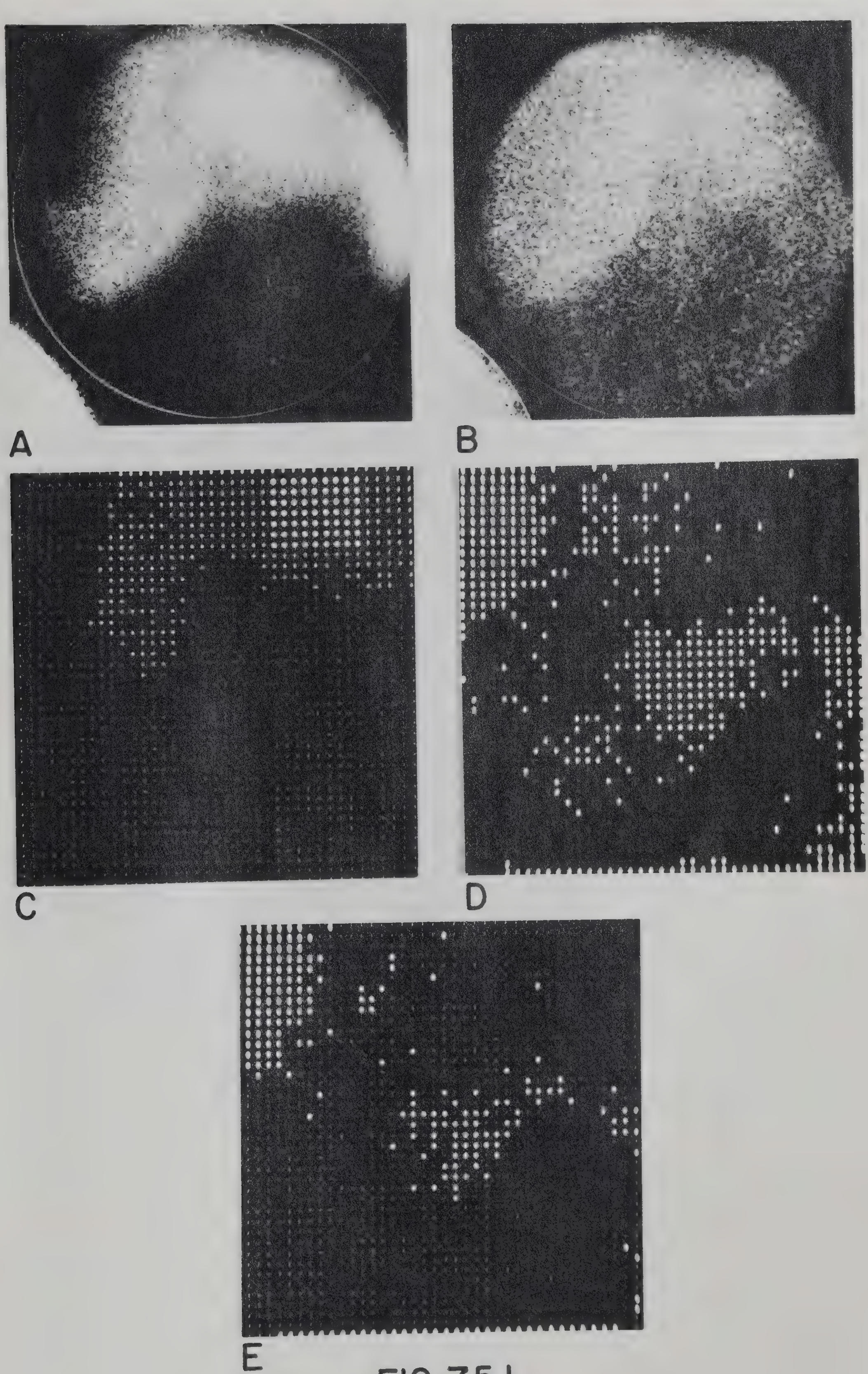
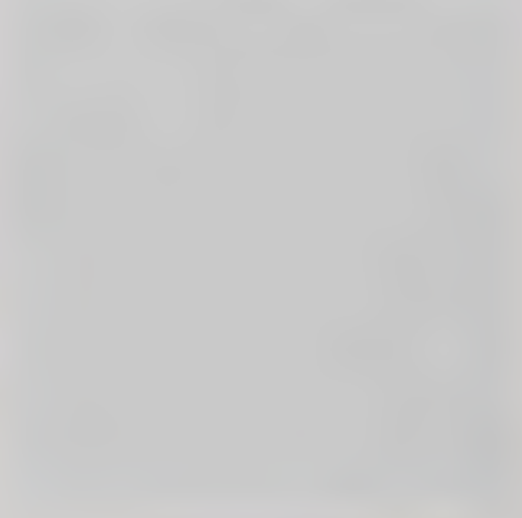


FIG. 7.5.1



A problem, which occurred with unknown frequency, was the presence of barium in the transverse colon as a result of previous upper gastro-intestinal investigation barium study or incompletely evacuated barium enema. If the transverse colon overlaps the pancreas in these patients, there would be significant absorption of radioactivity and apparent pancreatic abnormality.

Unfortunately the cases which were suspected of having this type of abnormality were not confirmed by repeat examination and were added to those of the 'false positive' group.

CHAPTER 8

CLINICAL APPLICATION AND RELIABILITY OF PANCREAS SCANNING

Early workers using conventional rectilinear scanning techniques were generally cautiously enthusiastic about the diagnostic accuracy of pancreas scanning (67,75,131,132), while some were non committal (134) and others pessimistic (135).

There is generally some difficulty in correlating the degree of pancreatic disease with the degree of abnormality present on the scan. Pancreatic carcinoma almost invariably results in an abnormal scan, but the degree of chronic, or acute and chronic, pancreatitis is difficult to correlate with the degree of morphologic abnormality demonstrated. Most focal lesions found at surgery can be identified in retrospect and authors often admit that lack of experience hampers their ability to interpret pancreatic scans (50).

Blau and Bender in their initial report of the clinical use of 75-Selenium-methionine for pancreas scanning, suggested that abnormalities could probably be visualized but had not yet examined patients with known pancreatic disease (66).

In 1964 Blau reported the first large series of pancreas scans, (8), describing his results in 58 patients. Interpretable scans were obtained in 85% with only about 50% positive scans in tumour (3 out of 6). No false-positive scans were reported and good results were suggested

in the diagnosis of active (acute or chronic) pancreatitis.

Haynie in 1964 (74) reported 37 usable scans obtained in 58 attempts. He was able to diagnose 7 of 11 patients with pancreatic carcinoma. Of the other four, three were interpreted as being equivocal (one carcinoma and two carcinoma of the ampulla) and the scan of one patient with carcinoma was interpreted as normal.

Tabern et.al. (80) reported 25 scans in 1965 and suggested good clinical results without specific figures given.

Berdine (75) in 1965 reported six positive scans which were subsequently proven to be pancreatic adenocarcinoma in a total of 29 patients with suspected pancreatic disease.

Sodee in 1966 (68) described his results in 251 patients and stated that 24 out of 25 carcinomas were reported as showing abnormal scans. He stressed that a normal scan indicated a normal pancreas and suggested the use of pancreatic scanning as a screening test. Most cases of acute and chronic pancreatitis in the study showed irregularly decreased radiopharmaceutical concentration and Sodee stated he could distinguish between pancreatitis and carcinoma in most cases.

Rodriquez-Antunez et.al. (73) in 1967 reported on 144 scans of which 107 were interpreted as normal. 103 were subsequently surgically or clinically verified to be normal. The four which were in error subsequently proved to have carcinoma. Of those 37 reported as abnormal 21 were

subsequently proven to have pancreatic disease (14 had carcinoma, 5 pancreatitis and 2 penetrating gastrointestinal ulcer with focal pancreatitis). 16 were assumed to be normal on clinical follow-up.

Again authors stressed that pancreatic scanning was a relatively reliable test to exclude pancreatic disease.

In 1968 Rodriquez-Antunez et.al. (136) reported 400 scans concluding that pancreatic scanning has a place in clinical practice to exclude the presence of pancreatic disease.

In 1968 Beck et.al. (97) reported 200 scans using the gamma camera and 4096 analyzer with digital subtraction of the liver activity. 125 scans were subjected to analysis. 16 patients had carcinoma of the pancreas and all 16 had abnormal scans consistant with this diagnosis. Unfortunately, the differentiation between carcinoma and pancreatitis was considered very difficult and could not usually be made on the basis of the scan alone. Of those 29 cases which were subsequently proven to have normal pancreases, one scan showed an apparent localized abnormality.

In a series of cases reported from Japan (137), involving 137 patients, there was only one false-negative and three false-positive scans. 43 of 44 cases of pancreatic carcinoma had scan images consistant with carcinoma.

This study suggested that pancreatic scanning is one of the most useful methods for diagnosing carcinoma of the pancreas. The authors suggested that scanning was not satisfactory in the diagnosis of pancreatitis as the degree of abnormality seen on the scan very often did not agree with clinical and laboratory evidence.

Riccobono (128) in reporting 225 scans also suggested that a normal scan is significantly more reliable than an abnormal one. Of the 22 cases carried out with the Anger camera (without subtraction) visualization was felt to be as good as or better than that obtained with the rectilinear scanner with considerable saving in time.

A report from Italy (133) of 30 cases, of which 20 were done with subtraction, on a rectilinear scanner suggested that subtraction techniques increased diagnostic capabilities.

Fink et.al. (94) in 1969 reported the results in 109 patients using dual channel scanning and color dot scan presentation. They suggested a relatively high false-positive rate of 18% in patients with normal pancreases. Eight of ten patients with carcinoma showed abnormal pancreas scans consistant with that disease. Twelve of nineteen patients with chronic pancreatitis showed abnormalities in the scan.

In 1968 Eaton et.al. (138) evaluated selective hypotonic duodenography, selective celiac axis angiography,

routine barium examination of the upper gastrointestinal tract and pancreas scanning, in the diagnosis of pancreatic disease in 45 patients. Three of the four procedures were performed on each patient. Eleven had normal pancreases, eleven had chronic pancreatitis or acute and chronic pancreatitis, nine had periampullary carcinoma, five had carcinoma of the body and tail of the pancreas, three had pseudocyst of the pancreas, three had papillitis, two had choledocholithiasis and one pericholecystic inflammatory mass.

Scanning was performed in 43 cases with 72% correct diagnosis, 19% false-positive diagnosis and 9% false-negative diagnosis. In comparison selective angiography showed 38% false-negative results.

It was concluded that pancreatic scanning was found to be the most sensitive of methods in the diagnosis of pancreatitis. False-positive diagnoses were the main drawback while positive scans were largely non specific in appearance. The authors pointed out the disadvantages of; expense, duration of the procedure and lack of general availability. Recommended applications by these authors, of the four diagnostic procedures, included: a) scanning and selective angiography for suspected tumour of the body and tail of the pancreas, and b) scanning and hypotonic duodenography for pancreatitis.

They suggested that scanning was correct in 90% of cases in which chronic pancreatitis was finally diagnosed.

Rodriquez-Antunez et.al.(139) in 1968 compared the diagnostic accuracy of celiac axis arteriography with liver and pancreas scanning. In 70 cases, in which both pancreatic scan and celiac axis arteriography were performed, no significant difference in the diagnostic accuracy of one method over the other was seen. They concluded that pancreatic scanning is preferrable to celiac axis arteriography in the diagnosis of pancreatic disease because, having the same degree of accuracy, it is easier to perform.

In 1968 Deininger and Sielaff (140) compared scanning with clinical and routine roentgenologic methods (excluding angiography). They concluded that pancreatic scanning was the preferred method of diagnosis in carcinoma of the pancreas.

Baum and Howe (141) concluded that hypotonic duodenography, percutaneous cholangiography and pancreas scanning were the most useful diagnostic procedures available for the diagnosis of pancreatic disease.

CHAPTER 9

RESULTS AND CLINICAL CORRELATION

9.1 250 patients have been subjected to pancreas scanning during the past 2½ years. One hundred and fourteen have had sufficient follow-up for final clinical diagnoses to have been made . (The major problem encountered in the course of this investigation was difficulty in obtaining complete and accurate follow-up data).

Procedural errors, most of which were encountered early in the study reduced the number of scans available for immediate subtraction from 114 to 93, and for computer processing to 88.

An abbreviated scan interpretation (normal, abnormal or equivocal) was assigned to each of the original scintiphotos and, where applicable, to the 'immediate subtraction', and computer subtraction, for each case.

The scan interpretations were compared to the final diagnosis and the results of this comparison are shown in Table 1.

A scan interpretation was labelled 'correct' if:

- the scan was considered to show abnormality in morphology and/or function, and pancreatic disease was subsequently proven to be present, or

TABLE I, CLINICAL CORRELATION

Evaluation Technique	№ of Scans	Scan Diagnosis Compared to Final Diagnosis		
		correct	incorrect	equivocal
Original Scintiphotos	114	48 %	13 %	39 %
	(88)[°]	49 %	12 %	39 %
Immediate Subtract.	93	72 %	9 %	19 %
	(88)[°]	74 %	7 %	19 %
Computer Subtract.	88[°]	83 %	8 %	9 %

[°] A Group of 88 Scans were evaluated by all three techniques.

- the scan was considered normal and no evidence of pancreatic disease was present at surgery, follow-up or autopsy.

A scan interpretation was labelled 'incorrect' if:

- the scan was considered normal and pancreatic disease was present, or
- the scan was considered abnormal and pancreatic disease was not proven. (Some cases of pancreatitis will fall in this category when the scan was correctly interpreted as abnormal and the diagnosis could not be confirmed).

Scans were considered 'equivocal' when pancreatic morphology and/or function could not be assessed due to:

- incomplete visualization, e.g. as in some scintiphotos where liver overlap is present, or
- poor definition of pancreatic activity related to high adjacent background activity, e.g. due to activity in the bowel, kidney or gastric tumour.

Based upon the original scintiphotos alone, accuracy in diagnosis of the presence or absence of pan-disease was less than 50%. Improved visualization of pancreatic morphology, and thus an increased accuracy in

diagnosis, resulted from the use of dual radioisotope 'subtraction scanning', even with the simple technique using multi-channel analyzer and cassette tape recorder.

The computer method for pancreas scan processing, described in this thesis, are seen to provide still further improvement in accuracy of scan interpretation.

It must be emphasized that the scan interpretations were not made entirely objective as knowledge of the patients clinical history and investigations were often available and well known at the time of scanning. An attempt was made to remain objective in my approach to the interpretations but the intent cannot be guaranteed as being completely successful.

In any event, the primary purpose was to establish the relative merits of the various techniques of evaluation - one to the other - rather than to establish an absolute measure of their accuracy.

The results listed in Table 1 must be viewed, therefore, as a relative evaluation of diagnostic value of the techniques, rather than a list of absolute accuracies for each.

This approach was necessary as no impartial referee was available to interpret the scans. Despite these drawbacks I feel that the figures quoted probably also represent a realistic measure of the diagnostic value of the scan and data processing methods.

9.2 Carcinoma of the Pancreas

Fourteen cases of proven carcinoma of the pancreas were studied in this series. Ten had scans which were interpreted as abnormal, and consistant with the diagnosis of carcinoma, in all three methods of evaluation (scintiphoto, immediate subtraction and computer subtraction). One case was considered abnormal in the scintiphotos and immediate subtraction and for which the computer subtraction could not be performed. Three cases were considered equivocal in the scintiphotos but abnormal in both the immediate subtraction and computer subtraction.

An incidental finding of considerable interest was that 4 of the 14 cases of carcinoma of the pancreas presented with cervical lymphadenopathy as the primary symptom or sign.

9.3 False Positive Scans

False positive scans were considered to be present when any one of the evaluation techniques were considered positive and pancreatic disease could not be proven. There were nine false positive interpretations.

Four of these had to be evaluated on the basis of the scintiphotos alone. One had a metastatic adenocarcinoma of the second lumbar vertebra of unkown primary origin, one had carcinomatosis of unknown primary origin, one had an acute blastic leukemia and one had carcinoma of the lung with a normal pancreas at autopsy.

All three methods of evaluation were employed in the

remaining five cases. One had alcoholic cirrhosis and in this patient the presence of pancreatitis could not be proven, one had abdominal pain of uncertain etiology and diabetes of many years duration, two had diabetes of late onset and one patient had gastritis, obesity and mild diabetes of indeterminate duration.

It is apparent that the first of two of these 'false positive' interpretations could actually be correct, as both patients died with carcinomatosis and no post-mortem examination performed. The primary site was never established and, of course, the pancreas is suspect.

It is of possible significance that four false positive scans were associated with diabetes. There is a suggestion, on the basis of these results, that diabetes may be associated with a scan appearance similar to that seen in chronic inflammatory disease of the pancreas (see Section 7.3).

9.4 The Investigation of Patients with Obstructive Jaundice and Other Signs and Symptoms of Carcinoma of the Pancreas

A. Carcinoma of the Pancreas

Eight patients who presented with obstructive jaundice were subsequently proven to have carcinoma of the pancreas. The pancreas scan was abnormal in all eight cases. Five scan images showed localized defects and three showed generalized decreased and irregular radioisotope uptake.

Case I: (Figure 7.2.1)

A 67 year old male investigated for cervical lymphadenopathy proven to be metastatic anaplastic carcinoma showed no primary lesion on complete respiratory, gastro-intestinal and renal investigation.

A pancreas scan was abnormal showing decreased and irregular radioisotope concentration in the head of the pancreas. A carcinoma of the cecum was suspected however and a lower abdominal laparotomy performed but no abnormality was found. The patient became jaundiced four months after the pancreas scan and a percutaneous transhepatic cholangiogram in association with hypotonic duodenography suggested neoplastic involvement of the distal choledochus. A repeat laparotomy disclosed carcinoma of the head of the pancreas.

Case II: (Figure 9.4.1)

A 49 year old male was investigated for vague upper abdominal pain and the gradual onset of obstructive jaundice and ascites. A routine upper gastro-intestinal series was normal but a pancreas scan revealed widening of the porta hepatis in direct continuity with a localized area of decreased radioisotope concentration along the superior aspect of the head of the pancreas. The remaining pancreatic tissue showed relatively normal uptake of radioisotope. Abdominal laparotomy revealed carcinomatosis and

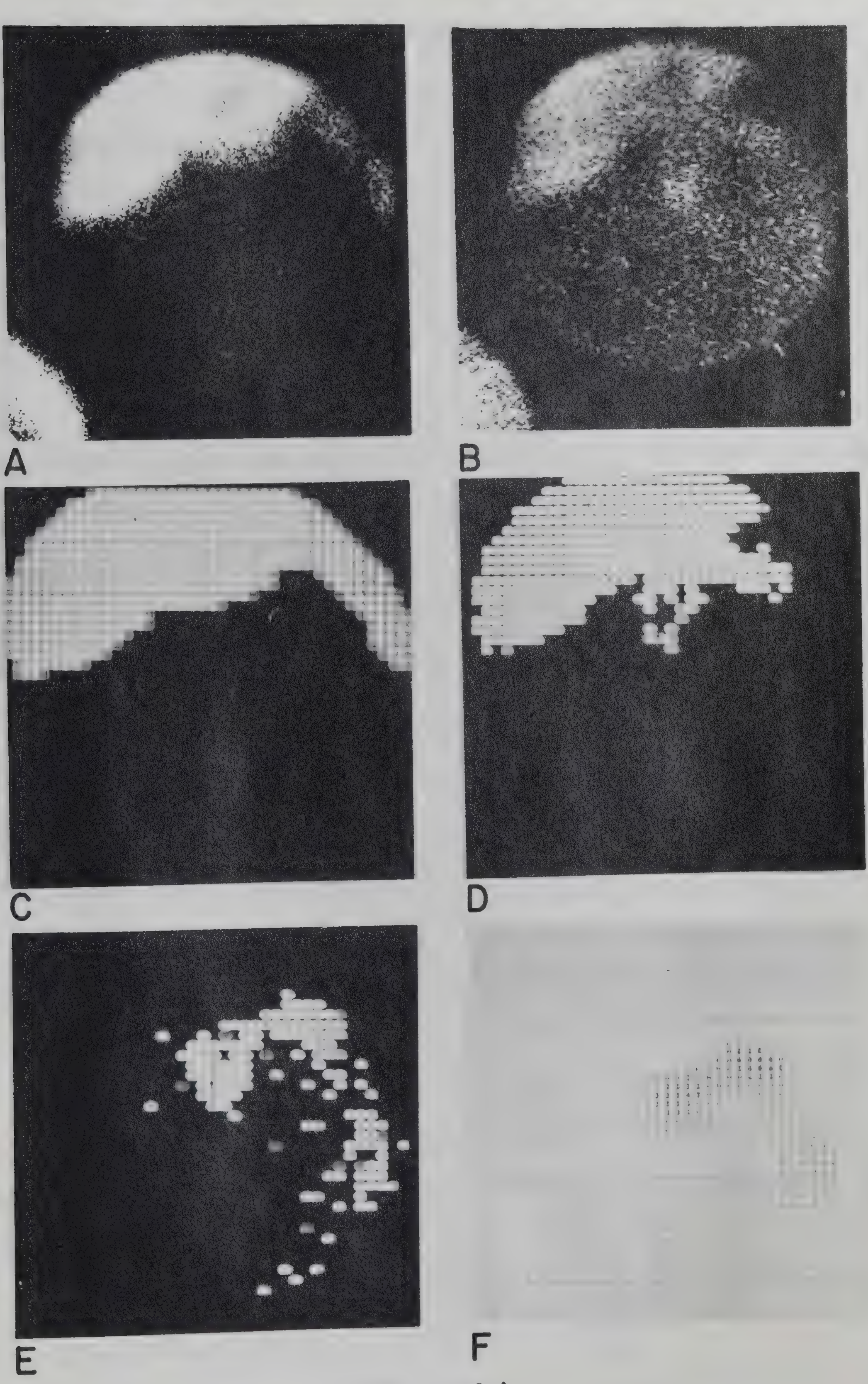


FIG. 9.4.1

ascites with extensive involvement of the porta hepatis and bile duct by carcinoma which also extended into the head of the pancreas. It was not determined with certainty whether the primary lesion arose in the common bile duct or in the head of the pancreas.

Case III: (Figure 9.4.2)

An 80 year old female developed abdominal pain and a duodenal ulcer was diagnosed although no abnormality was found in the upper gastro-intestinal series. The patient presented six weeks later with jaundice and fatigue. An upper gastro-intestinal series showed mucosal irregularity and rigidity in the postbulbar duodenum.

A pancreas scan demonstrated decreased and irregular uptake of radioisotope suggestive of extensive neoplastic disease or severe pancreatitis. Laparotomy revealed a large carcinoma of the head of the pancreas.

B. Carcinoma of the Ampulla of Vater, Bile Ducts and Gallbladder

Three patients presented with obstructive jaundice and with clinical symptoms suggestive of carcinoma of the pancreas. In all cases the pancreas scan was normal in appearance.

Case IV: (Figure 9.4.3)

A 74 year old male had a three week history of pain-

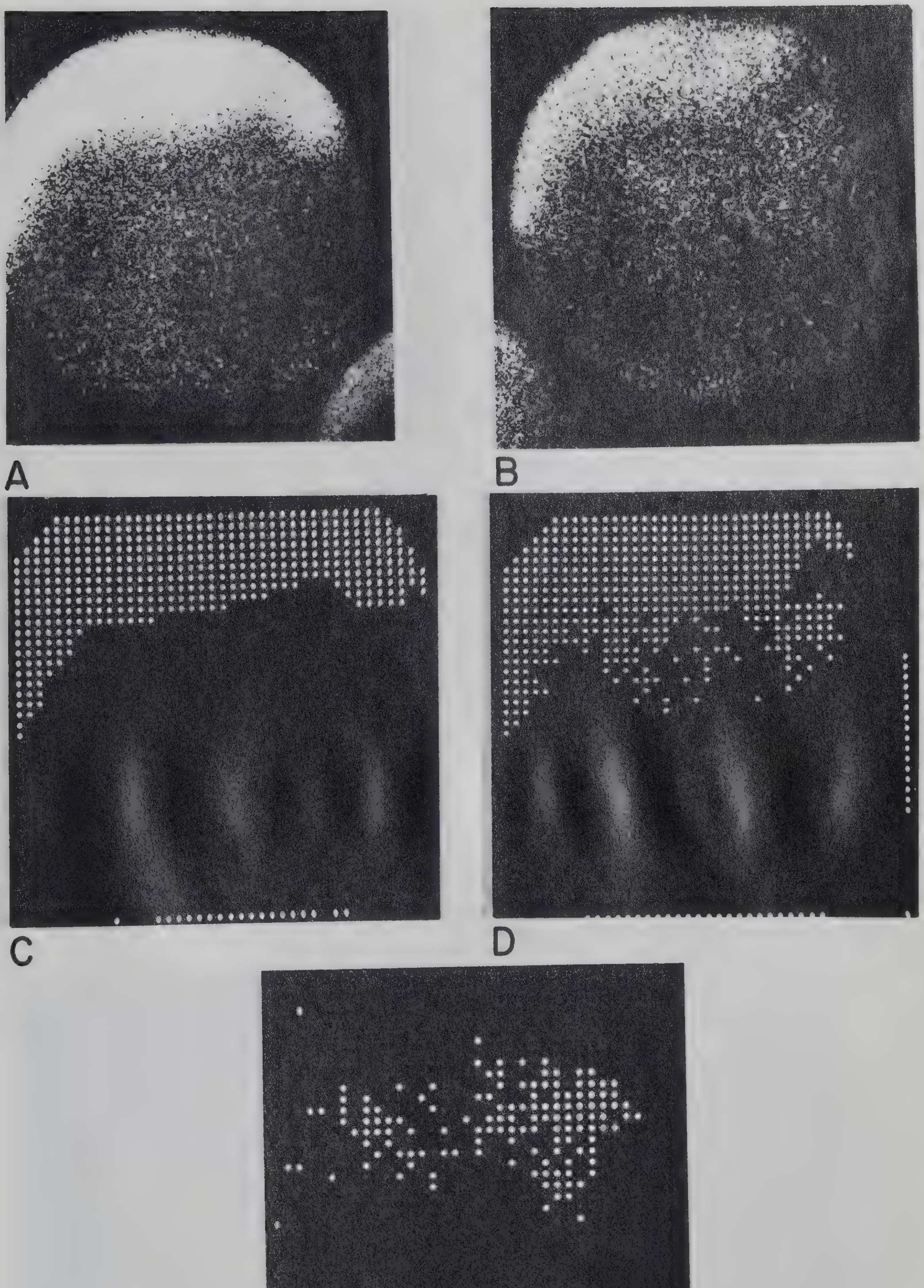


FIG. 9.4.2

[illegible]

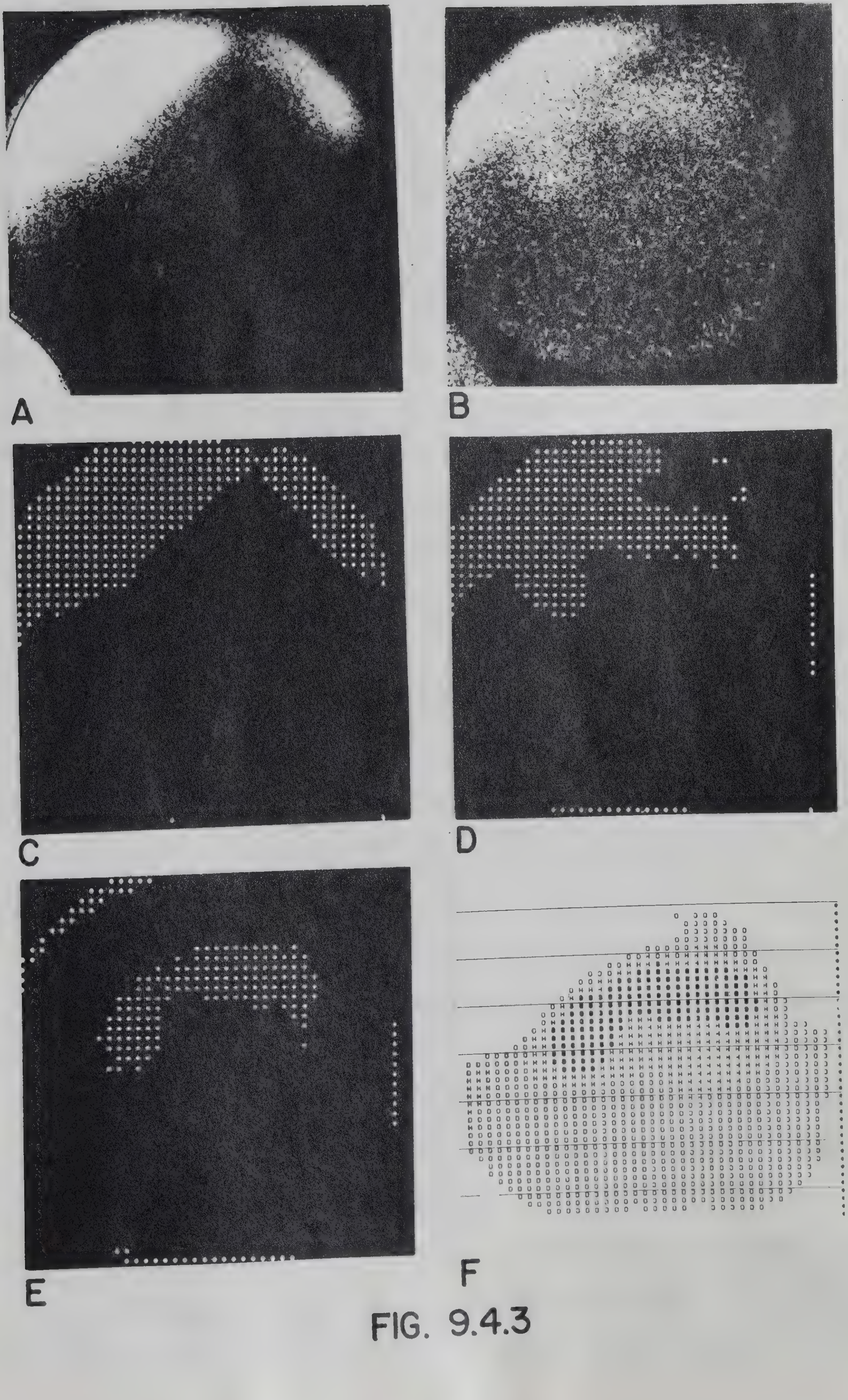


FIG. 9.4.3

less jaundice associated with moderate anorexia and weight loss.

The pancreas scan was considered completely normal. Percutaneous transhepatic cholangiography combined with selective hypotonic duodenography demonstrated a small mass in the region of the ampulla, felt to represent a small ampullary carcinoma. At laparotomy a 2 cm carcinoma of the ampulla of vater was found.

Case V: (Figure 9.4.4)

A 58 year old male developed malaise, nausea and painless jaundice over several weeks.

Upper gastro-intestinal examination showed evidence of extrinsic pressure on the duodenum without direct invasion of the duodenal mucosa and a pancreas scan was normal. At laparotomy, a large adenocarcinoma of the bile ducts without involvement of the pancreas was found.

Case VI: (Figure 9.4.5)

A 72 year old female presented with vague right upper quadrant pain and progressive jaundice of six months duration.

Routine gastro-intestinal X-rays were normal but a percutaneous transhepatic cholangiogram revealed uniform dilatation of the ductal system up to the middle segment of the common duct where complete obstruction was encountered.

A pancreas scan showed no abnormality. Laparotomy revealed inoperable carcinoma of the gallbladder without involv-

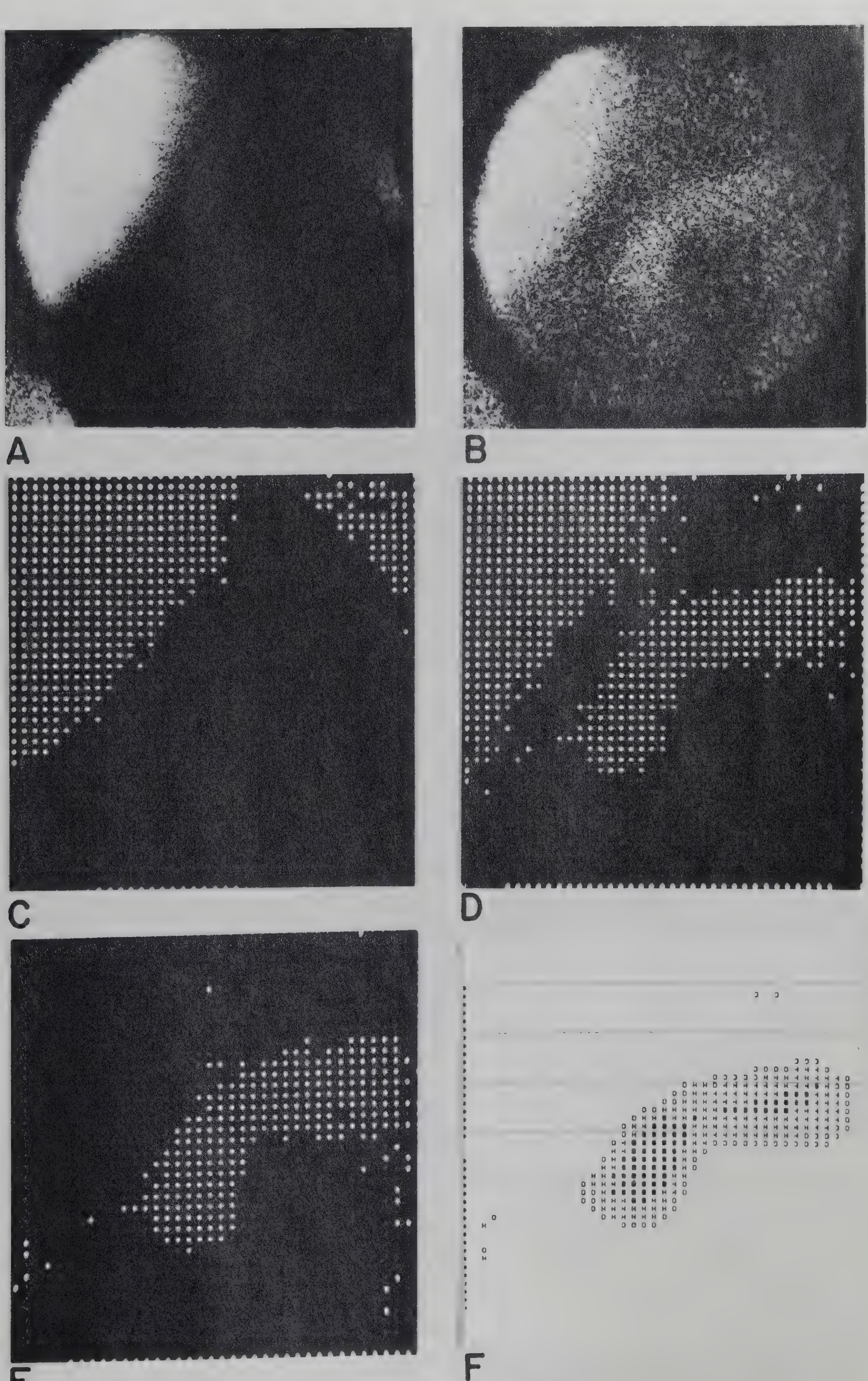


FIG. 9.4.4

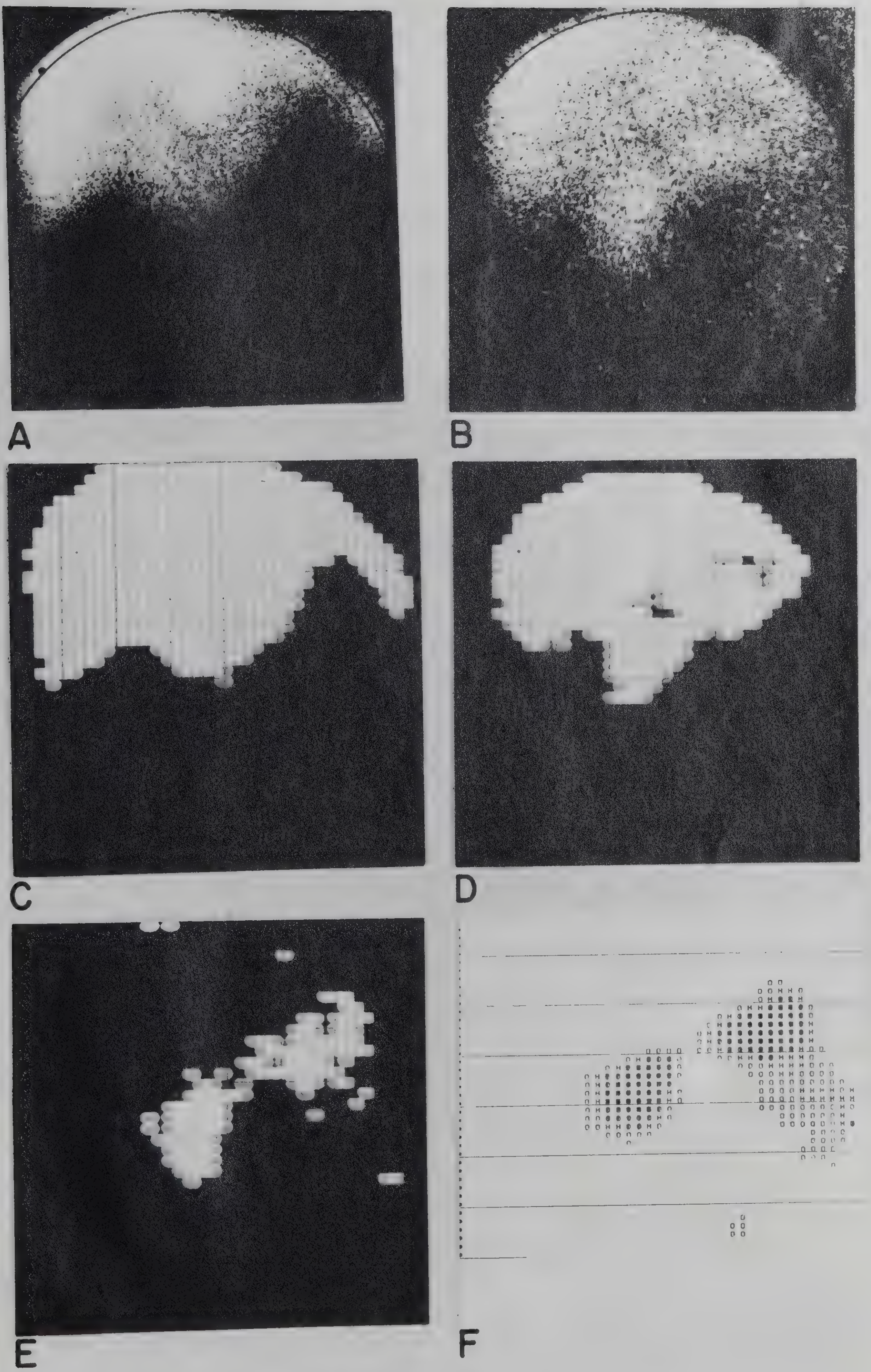


FIG.9.4.5

ement of the pancreas.

C. Serum Hepatitis

Case VII:

A 67 year old male was admitted for investigation of painless obstructive jaundice of two weeks duration.

A routine upper gastro-intestinal series suggested carcinoma of the head of the pancreas but a pancreas scan appeared normal. Selective hypotonic duodenography was then performed and showed no abnormality.

The patient gave a vague history of 'needles' for an illness several months previously. His SGOT was 2100 units on admission. He was treated conservatively and his elevated bilirubin and SGOT resolved spontaneously over three weeks. The patient was discharged with a diagnosis of homologous serum hepatitis with cholestatic jaundice.

D. Common Bile Duct Stones

Three patients presented with 'silent' choledocholithiasis and jaundice. The pancreas scans obtained on all these patients were normal.

Case VIII: (Figure 9.4.6)

A 58 year old female was investigated for a two month history of jaundice with vague right upper abdominal pain and vomiting. She had been mildly febrile during this time and had received antibiotics. The gastro-intestinal

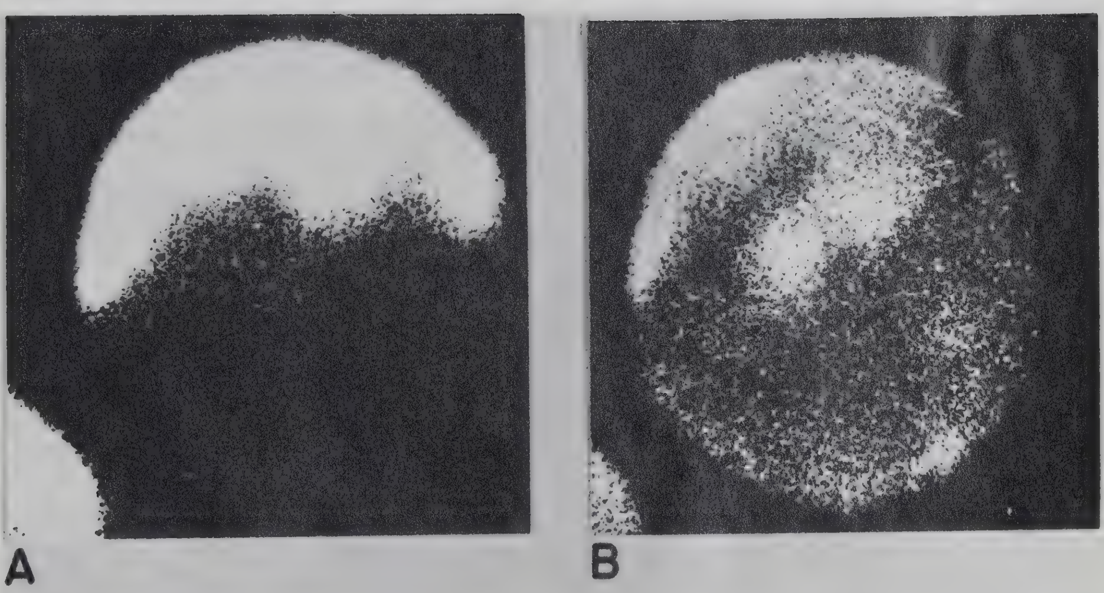


FIG. 9.4.6

series was normal as was the pancreas scan.

Laparotomy revealed cholecystitis, cholecystolithiasis and choledocholithiasis. There was evidence that the gallbladder had recently ruptured.

E. Chronic Pancreatitis Associated with Jaundice

Two patients investigated for recurrent obstructive jaundice were presumed to have chronic pancreatitis secondary to biliary disease. The pancreas scans for both patients were abnormal.

Case IX: (Figure 9.4.7)

A 30 year old female had a history of at least five episodes of abdominal pain and jaundice over an eight-year period following cholecystectomy for choledocholithiasis. She was investigated during a symptom free period.

Selective hypotonic duodenography and intravenous cholangiography were normal. A pancreas scan revealed markedly decreased and irregular uptake of radioisotope in the region of the pancreas.

During a subsequent episode of abdominal pain she had well documented evidence of pancreatitis and it was felt that she was suffering from chronic recurrent pancreatitis secondary to previous biliary disease.

F. Carcinoma of the Pancreas Without Jaundice

Six patients were found to have carcinoma of the

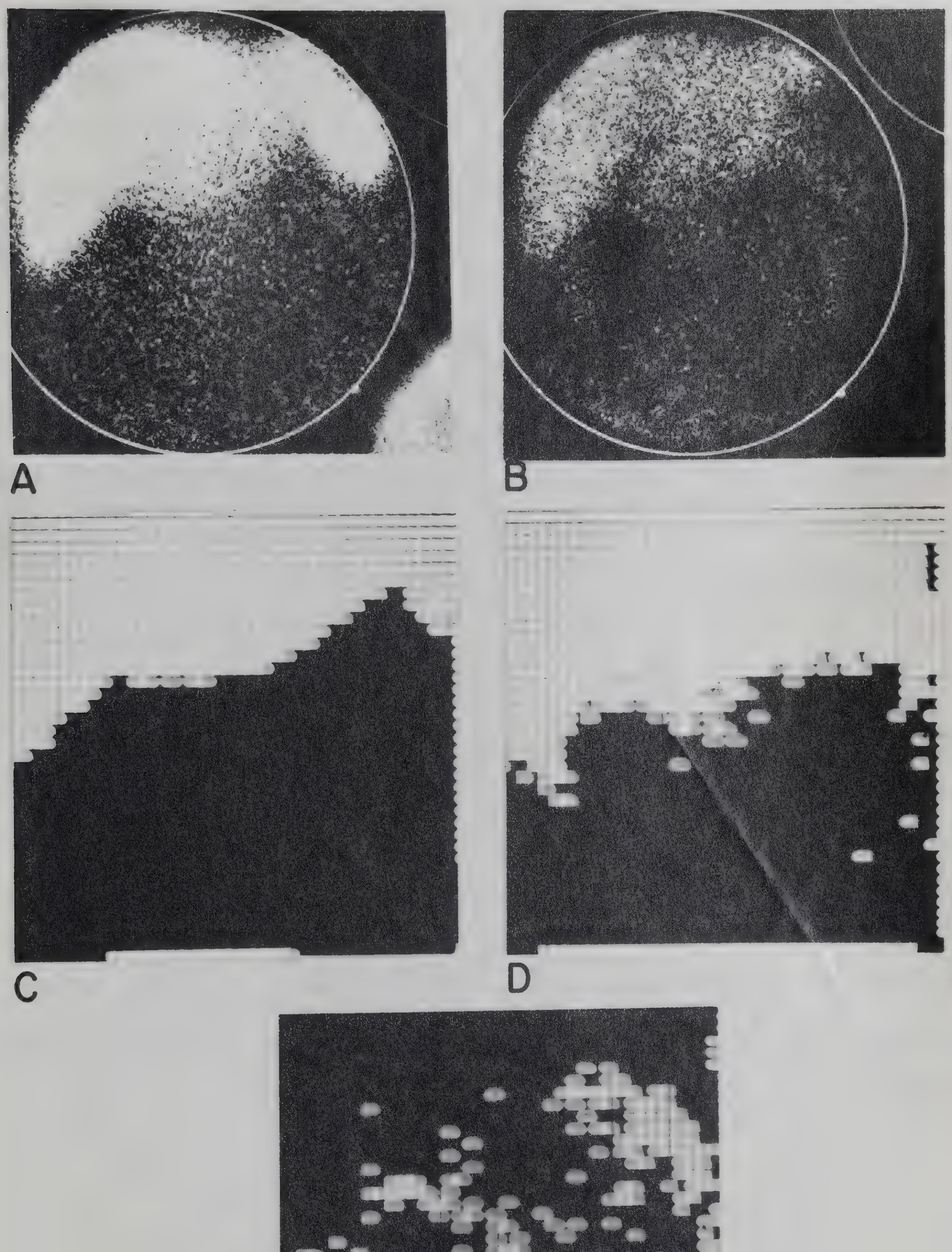


FIG. 9.4.7

pancreas without obstructive jaundice. One patient was investigated for recurrent thrombophlebitis and one for depression and weight loss. At laparotomy both these patients were found to have carcinoma of the body of the pancreas.

Four patients were investigated for abdominal pain and of these, two had carcinoma of the body of the pancreas and two carcinoma of the head of the pancreas. These latter two patients did not have jaundice due to previous cholecystoduodenostomy for pancreatitis in one case and previous choledochoduodenostomy for pancreatic pseudocyst in the other.

The scans were abnormal and consistant with the presence of pancreatic neoplasm in all six patients.

G. Discussion

Abnormal pancreas scans were obtained in fourteen patients with proven carcinoma of the pancreas. Unfortunately, the scan appearance with carcinoma is not completely diagnostic, as chronic pancreatitis can produce the same type of scan abnormality. It has been my experience however, that carcinoma of the pancreas produces much more distortion of pancreatic architecture and a more irregular distribution of radioisotope than chronic pancreatitis in which pancreatic morphology is relatively intact and radioisotope concentration is often severely, but fairly uniformly, decreased. Two patients with well-documented evidence of chronic pancreat-

itis and intermittent jaundice were discovered to have abnormal pancreas scans of this type.

Seven patients presented with obstructive jaundice and were subsequently proven to have extra-pancreatic disease as the basis of their biliary obstruction. These patients had normal pancreas scans and, in fact, pancreas visualization was considered superior to that seen in most normal patients. The reason for this apparent enhanced visualization in the presence of jaundice is not known, but it is of considerable diagnostic importance, as it virtually rules out pancreatic disease. There is a possibility that this phenomenon is related to a normal pancreatic uptake of radioisotope and a decreased uptake in the liver due to depression of hepatic metabolism. (It is not known for certain if decreased hepatic uptake of 75-Selenium-methionine occurs in obstructive jaundice.) However, the overall scan appearance and the count rates obtained, suggest that increased pancreatic uptake actually does occur in these patients and if this is true, several factors might be considered in order to explain the scan appearance:

a) It is possible that depression of hepatic metabolism reduces accumulation of radioisotope in the liver thus making more available for pancreatic utilization.

b) Increased blood supply to the pancreas related to decreased hepatic blood flow in

obstructive jaundice is also possible,
again providing more radioisotope to the
pancreas.

It has been shown experimentally that only about 7.5% of hepatic uptake of 75-Selenium-methionine is excreted in the bile (20). A reduction of background activity in the small bowel is unlikely therefore, to account for enhanced pancreatic visualization when biliary obstruction is present.

It also seems unlikely that increased pancreatic uptake of 75-Selenium-methionine occurs, in jaundice, due to altered pancreatic metabolism related to the direct effects of elevated bilirubin.

It is not known at present if this apparent enhanced pancreatic visualization occurs in patients with non-obstructive jaundice since such patients are seldom referred for pancreas scans.

9.5 Conclusions

It has been demonstrated that pancreas scanning provides the ability to visualize gross pancreatic morphology, and to qualitatively evaluate exocrine pancreatic function, in an atraumatic fashion.

A normal scan is highly indicative that the exocrine pancreas is structurally and functionally intact. The incidence of false negative scans is certainly less than 5% and these cases tend to be patients with relatively benign

disease (e.g. mild pancreatitis) or with disease which presents a fairly well defined clinical picture (e.g. insulinoma and non Beta islet-cell adenoma associated with the Zollinger-Ellison syndrome). Pancreas scanning, therefore, can be employed as a screening procedure to determine the absence of exocrine pancreatic disease.

An abnormal scan is strong evidence of pancreatic pathology. The abnormalities demonstrated in pancreatitis and in carcinoma are, however, of similar appearance and are difficult to differentiate when extensive parenchymatous disease is present. Artefacts, as discussed in Chapter 7 can produce false positive scans, and for this reason, a positive scan must be confirmed if other firm evidence of pancreatic disease is not available.

The advantages of the procedure probably outweigh the disadvantages. It is safe; no untoward effects have been observed in any of the 250 patients so far studied, nor have any been reported in the literature.

The procedure is painless and only a few patients complained of discomfort when required to lie still. The radiation dose delivered to the patient is within acceptable limits and well below that delivered by many diagnostic roentgenologic procedures. Repeated scans can be performed to evaluate the course of pancreatic disease in selected patients.

There are disadvantages which limit general avail-

ability of pancreas scanning. The expense is considerable and the cost of radioactive materials required for a single scan is in excess of one hundred dollars. The time involved is longer than for other scanning examinations; about 45-60 minutes is required. Considerably more time is required of the attendent personnel for processing and data reduction. Computer time is expensive and difficult to obtain. The multi-channel analyzer, cassette tape recorder, data processor and paper tape printer are not standard equipment, and are expensive.

On the basis of the clinical correlation presented, and the demonstrated safety of the procedure, it is concluded that pancreas scanning, including subtraction techniques as outlined in this thesis, is a useful and justified diagnostic examination in those patients undergoing investigation for possible pancreatic disease.

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